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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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WILLIAM T. FITTS,
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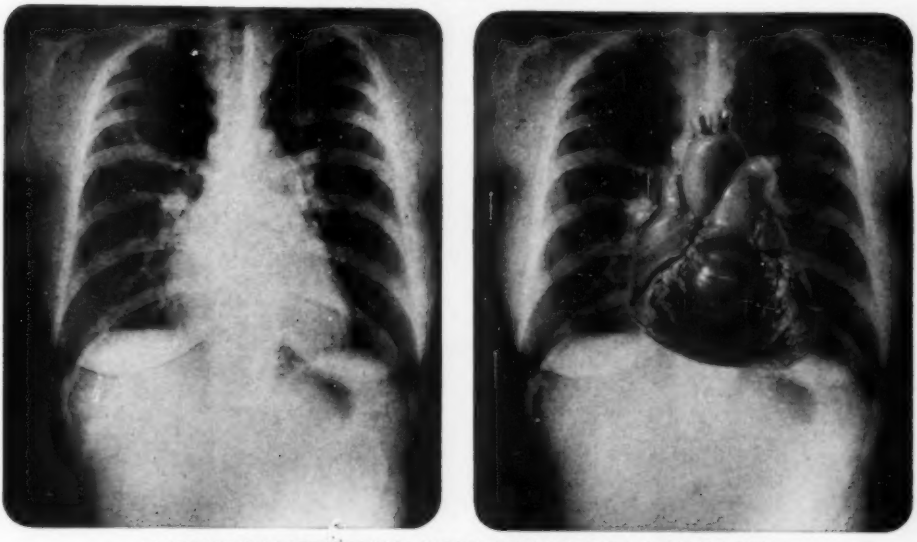

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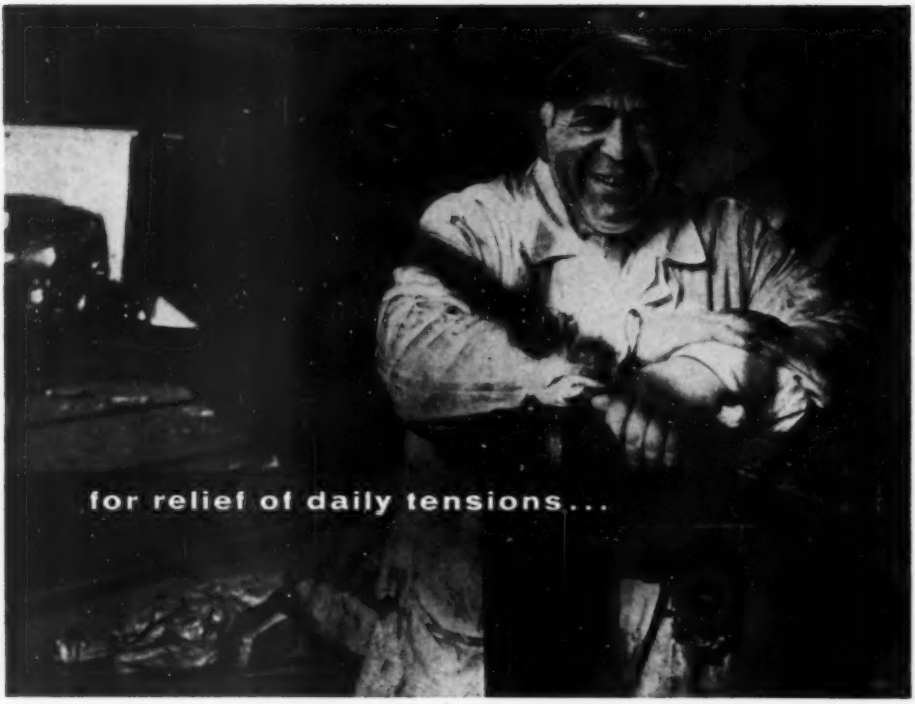

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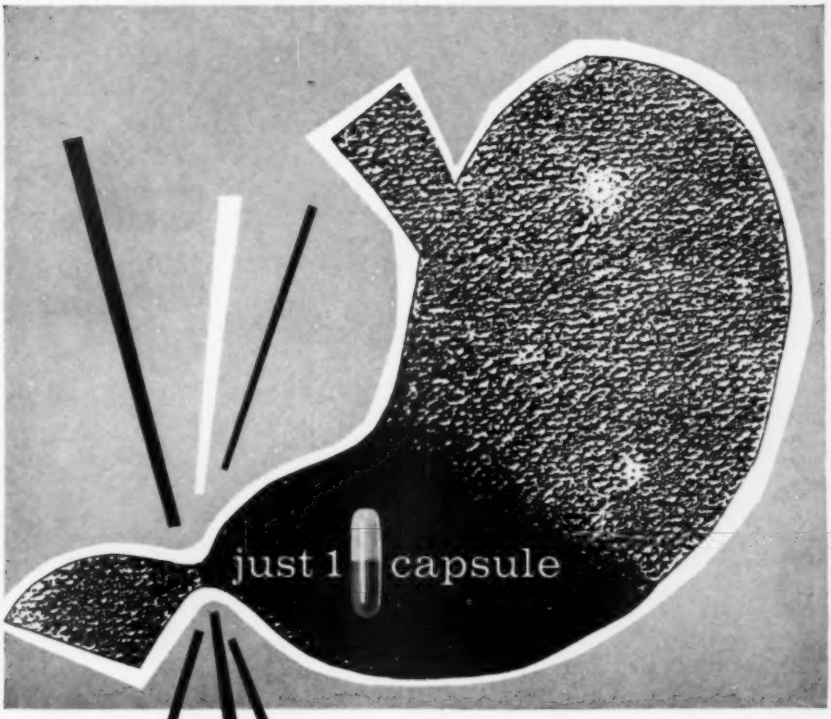

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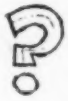
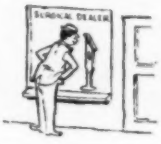
measurements *the whole world over.* Do you own a Baumanometer?  If not,

why not get a nice new one at your Surgical Dealer's. 

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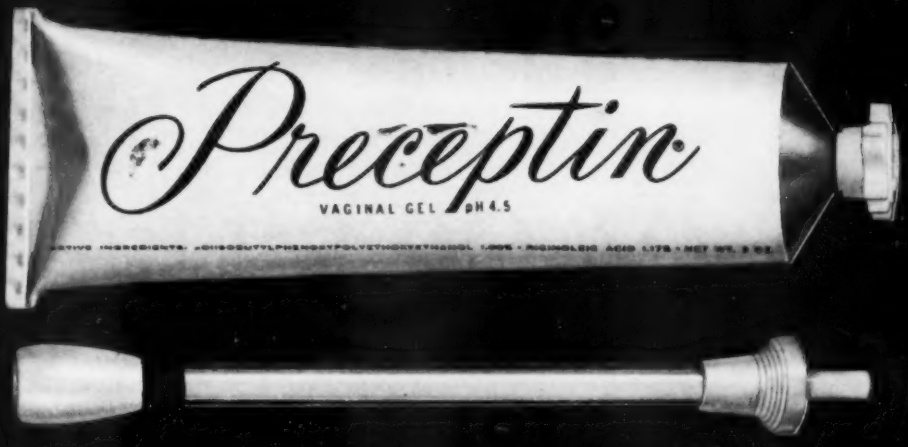

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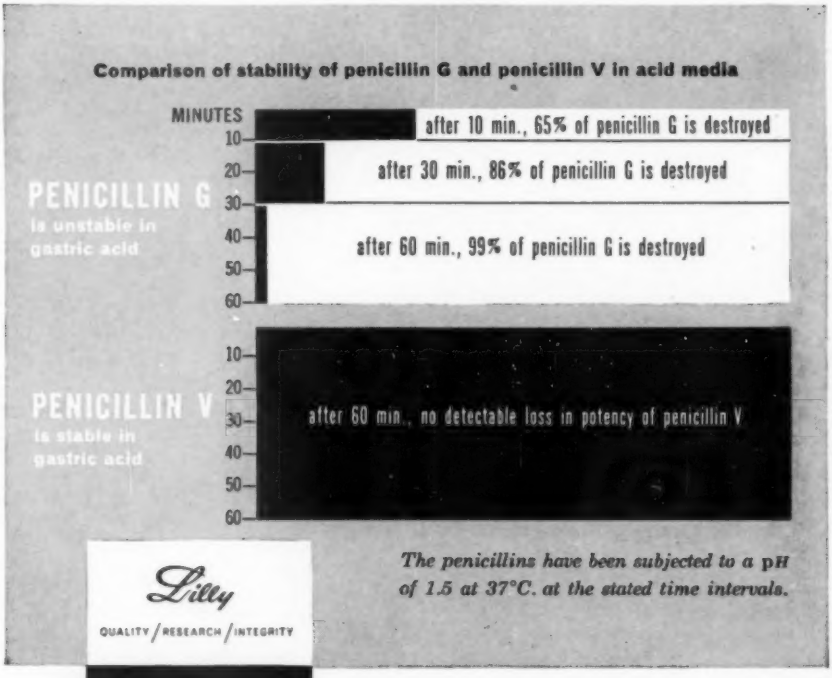
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BULLETIN OF
THE NEW ACADEMY
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VOL. 33, NO. 3 MARCH 1957

THE PLACE OF ADRENALECTOMY IN THE TREATMENT OF SEVERE ARTERIAL HYPERTENSION*

CHARLES C. WOLFERTH, WILLIAM T. FITTS, WILLIAM A. JEFFERS and ALFRED M. SELLERS

THE study to be reported here has been carried on over six and one-half years and progress reports have been made from time to time.[1-4] Its purpose has been to explore the possibility of developing a useful operative procedure for lowering blood pressure in patients with so-called essential hypertension refractory to other methods of treatment. We had not been content with the limitations of improvement observed following thoracolumbar sympathectomy although our results,[5] so far as we have been able to determine, are similar to those reported by Smithwick in his much larger series. It seemed important to discover whether adrenalectomy could achieve a place in the treatment of hypertension, and if so, how extensive it would have to be and whether it should be combined with sympathectomy. We were encouraged to

* Presented in condensed form by Dr. Wolferth at the Twenty-Ninth Annual Graduate Fortnight of The New York Academy of Medicine, October 15, 1956.

From the Edward B. Robinette Foundation, Medical Clinic and the Surgical Service of the Hospital of the University of Pennsylvania, Philadelphia, Pa.

This investigation has been supported in part by research grants from the National Heart Institute, the U.S. Public Health Service (H. 388); the Squibb Institute of Medical Research; Eli Lilly & Company; Ciba Pharmaceutical Products, Inc.; and Merck and Company, Inc.

TABLE I—TYPES OF OPERATIONS PERFORMED AND SURVIVAL TO PRESENT TIME

	Operated	*Living*	*Dead*
Subtotal Adrenalectomy Alone	13	4	9
Subtotal Adrenalectomy and Peet Sympathectomy	1	0	1
Subtotal Adrenalectomy and Adson Sympathectomy	64	46	18
Total Adrenalectomy and Adson Sympathectomy	76	59	17
Total or Subtotal Adrenalectomy and Smithwick Sympathectomy	14	9	5
TOTAL	168	118	50

proceed by the preliminary report of one case in which severe hypertension had been relieved by almost total adrenalectomy.[6]

When this study was instituted the development of effective drug antihypertensive therapy had scarcely begun. The blood pressure lowering effects of Rauwolfia drugs were not known, at least in this country, and their combinations with other agents such as ganglionic blocking drugs and hydralazine so frequently employed today were still further beyond the horizon. Had such methods of treatment been available sooner, many of our patients subjected to operation would doubtless have exhibited enough response to have been continued on conservative treatment. That this would have been the course of events is demonstrated by the marked reduction in the number of operations carried out during the past two years. But not all patients, at least in our experience, respond satisfactorily to vasodepressor therapy. Some are intolerant of effective drug combinations and others, although reasonably tolerant, show little blood pressure response. These form the reservoir from which patients are now being selected for operation.

It was recognized at the beginning of this study that if adrenalectomy proved useful in the treatment of hypertensive disease, there must nevertheless be limits to its applicability. The data to be reported here must necessarily include the results of what we would now regard as errors of judgment in the acceptance of patients. We learned early that the operation should be performed in two stages, usually ten days or more apart and that patients with advanced renal failure should not be accepted. In fact very few with a PSP excretion of less than 15 per cent

in 15 minutes or a BUN consistently above 20 mg. per cent (unless caused by congestive heart failure) have benefited from the operation. Temporal age and senescence do not necessarily go hand in hand, especially in hypertensive patients, but in general, the results in those more than 55 years old have not been good from the viewpoint of blood pressure response and the occurrence of vascular accidents. We have tried to avoid operation for at least three months after even minor cerebral or coronary vascular seizures and have not recommended it in those with clinically important residua. The importance of patient cooperation was emphasized by an unnecessary death from failure to follow instructions concerning replacement therapy.

Number of Patients Operated On and Types of Operations Performed

These data are presented in Table I which includes the record of survival to date in each group. The poor survival among the patients submitted to adrenalectomy alone is due partly to the fact that these were "desperation" cases. But in three, as we were to learn later, renal failure was too far advanced for improvement in the hypertensive state to occur. In two, the combination of a single stage operation and, by later standards, inadequate replacement therapy during the operative and postoperative periods were thought to be mainly responsible for death. In one patient in whom an estimated 25 per cent of one adrenal was left in situ, operation appeared to exert no influence upon the course of hypertensive disease. The patient mentioned previously who died because of failure to cooperate in replacement therapy, had shown promise of an excellent result.

Although the four patients who have survived subtotal adrenalectomy were all greatly improved and have maintained their improvement over periods now averaging about six years, the early results in none equalled those of our first patient who had previously been subjected to thoracolumbar sympathectomy with only temporary modest improvement. Following subtotal adrenalectomy with approximately 10 per cent of one adrenal left in situ, this patient was completely relieved of severe hypertension in two months (which has never recurred) and reverted from practically complete disability to rapid complete rehabilitation. This response demonstrated that the addition of subtotal adrenalectomy to thoracolumbar sympathectomy is, at

least upon occasion, capable of converting failure in the treatment of hypertension to success. Moreover, it suggested, in the light of our subsequent experience with adrenalectomy alone, that sympathectomy had probably contributed something to the successful result. Accordingly it was decided to try further the effect of combining sympathectomy with adrenalectomy.

The Adson procedure (save for removal of the celiac ganglion) was chosen for trial first because it could be carried out through the incision employed for adrenalectomy and in the hands of a surgeon familiar with the procedure, added no more than 15 minutes of operating time in each stage. The fall in blood pressure, after the second stage of the operation was completed, was found to be more prompt than after adrenalectomy alone. Moreover, the characteristic postural fall in pressure that develops after sympathectomy, although at least a temporary nuisance in those with an excellent blood pressure response, appeared to be an advantage in those in whom the fall in pressure in supine or sitting positions was less satisfactory. After observing a series of patients who had been subjected to the combined operation, we became unwilling to return to adrenalectomy alone. We felt that we could justify this policy upon the basis that if adrenalectomy proved ineffective in any patient, he might derive at least some benefit from sympathectomy.

As is shown in Table I, thoracolumbar sympathectomy was performed in 14 patients. In several of these, adrenalectomy was carried out after the results of sympathectomy alone or in combination with unilateral adrenalectomy, the Leriche operation,[7] had not yielded satisfactory results. In others, thoracolumbar sympathectomy was performed in conjunction with adrenalectomy because of the assumption that extensive sympathectomy might help to lower pressure more effectively than limited sympathectomy. Our data however are not adequate to permit such a conclusion. In fact, we have no cases in which sympathectomy was done later than adrenalectomy and thus no direct evidence as to its value in supplementing adrenalectomy.

The possibility that some of the disappointing results were caused by failure to remove enough adrenal tissue led to a trial of total adrenalectomy combined with sympathectomy following the work of Thorn and associates[8] with total adrenalectomy. The record of survival of patients subjected to total adrenalectomy is slightly better than in those

TABLE II—DURATION OF FOLLOWUP OF 114 SURVIVING PATIENTS WITH TOTAL OR SUBTOTAL ADRENALECTOMY AND ADSON OR SMITHWICK SYMPATHECTOMY.

Less than 3 Months	3
3 - 6 Months	3
6 -12 Months	4
12-24 Months	15
24-36 Months	22
36-48 Months	27
48-60 Months	24
60-72 Months	10
72-84 Months	6
TOTAL	114

with subtotal adrenalectomy, but no significance is to be attached to these figures as evidence for superiority of total extirpation of the adrenals. The results of the two procedures have seemed essentially the same when no more than an estimated 5 per cent of adrenal tissue is left in situ in the subtotal procedure, save that, in general, more replacement therapy has been required following total adrenalectomy.

DURATION OF OBSERVATION FOLLOWING OPERATION

In Table II the duration of follow-up periods of the 114 patients who have survived the combination of adrenalectomy (total or subtotal) and sympathectomy (Adson type, 105, thoracolumbar sympathectomy, 9) is stated. The reduction in the number of operations performed during the past two years is shown in the table.

MORTALITY

The mortality among the 154 patients subjected to combined adrenalectomy and sympathectomy in relation to the Smithwick classification was as follows: Group II, 51 patients of whom 47 are living and 4 dead; Group III, 38 patients of whom 27 are living and 11 dead; Group IV, 65 patients of whom 40 are living and 25 dead. The causes of mortality and time relation to operation are shown in Table III.

Patients who died within one month following the second stage

TABLE III—CAUSES OF DEATH OF 40 PATIENTS WITH COMBINED TOTAL OR SUBTOTAL ADRENALECTOMY AND ADSON OR SMITHWICK SYMPATHECTOMY IN RELATION TO SMITHWICK CLASSIFICATION (PRIOR TO OPERATION) AND TIME OF DEATH AFTER OPERATION.

Cause of Death	*Smithwick Classification*	*Time of Death After Operation*					
		1 Mo.	*1-6 Mos.*	*6-12 Mos.*	*12-24 Mos.*	*24 Mos.*	*Totals*
	II	2	0	0	0	0	2
Cerebral	III	0	0	0	2	1	3
Vascular	IV	2	3	1	3	4	13
							18
	II	0	0	0	0	1	1
Coronary	III	0	1	1	1	1	4
	IV	1	2	1	1	1	6
							11
	II	0	0	0	0	0	0
Uremia	III	0	1	0	0	0	1
	IV	0	2	1	0	1	4
							5
	II	0	0	0	1(e)	0	1
Other	III	0	1(c)	1(b)	1(f)	0	3
Causes*	IV	1(a)	0	0	0	1(d)	2
							6
TOTALS		6	10	5	9	10	

Other Causes*

(a) Hemorrhage, (b) Carcinoma, (c) Suicide, (d) Bleeding Ulcer, (e) Gastro-Intestinal Bleeding, Point of Origin not Determined, (f) Unknown.

of the operation (the two stages were usually carried out about ten days apart) were arbitrarily classified as operative mortalities. The one patient who died following profuse hemorrhage into the incision was undoubtedly an operative death. However it did not seem to us that operation was necessarily responsible for all of the four deaths from strokes and one from acute myocardial infarction which occurred within one month after operation. The deaths from uremia occurred in patients whose preoperative renal function was below the levels eventually established as adequate to permit operation. It is note-

worthy that not a single death in this entire series resulted from congestive heart failure. As the study progressed, our impression grew that the mortality rate diminished in patients who survived the first year after operation including those with the most advanced stages of hypertensive disease prior to operation. Table III shows that there were 21 deaths among 154 patients following adrenalectomy and sympathectomy during the first year after operation and 19 deaths among 133 patients in subsequent years. The total "patient-years" of observation one year or more after operation is roughly 2½ times that of the first year. Thus even if we subtract the six cases classified as "operative deaths" from the number who succumbed during the first year, the mortality rate is appreciably lower after the first year. Nevertheless the occurrence of some deaths among patients who had been doing well since operation, remains a matter for concern. It has become clear that control of blood pressure in hypertensives affords far from complete protection from lethal arterial episodes, especially in those with advanced deterioration prior to operation. In the early period after operation, certainly during the first month and perhaps during the first year, it is possible that marked reduction of arterial pressure below levels to which the patient had been accustomed, may be a factor of importance in precipitating vascular obstruction. However when acute cerebral damage or acute myocardial infarction occur long after operation, it seems necessary to assume that progression in vascular disease after operation has made such accidents possible. The work of Hafkenschiel and associates[9] on cerebral blood flow in some of our patients before and after operation indicates an amazing adaptation in resistance over a wide range in pressure with maintenance of constancy in flow. We have no data on coronary flow before and after operation. Electrocardiograms do not tend to show changes after operation that would appear to reflect increase of ischemia, save in the exceptional cases with symptoms suggesting an acute obstruction in the coronary circulation. But stenosis of a vessel might, if sufficiently advanced, cause local impairment of cerebral (or coronary) blood flow when the arterial pressure falls without affecting significantly the total blood flow. Slowing of flow at an initial point of stenosis in a vessel might favor thrombosis beyond that point. Furthermore, in the case of the coronary circulation, acute obstruction of an artery is not a necessary preliminary to acute infarction because

TABLE IV—BLOOD PRESSURE RESPONSES IN 114 PATIENTS SURVIVING TOTAL OR SUBTOTAL ADRENALECTOMY AND ADSON OR SMITHWICK SYMPATHECTOMY

Definition of Response

A. Blood pressure in range of 150/100 or less supine—Equal or less standing
B. " " " " " 150-180/100-110 " — " " " "
C. " " " " " 180-200/110-120 " — " " " "
D. " " " " " 200/120 or more " — " " " "

Blood Pressure Responses

		A	*B*	*C*	*D*	*No Data**
Smithwick	II	22	10	4	7	4
Smithwick	III	12	8	1	3	3
Smithwick	IV	14	9	6	7	4
TOTALS		48(4)**	27(5)	11(6)	17(12)	11(2)

* No data refers to patients operated on less than 6 months ago (5 cases) and those in whom inadequate observations on blood pressure have been obtained during the past 12 months (11 cases).

** The figures in parenthesis indicate numbers of patients receiving vasodepressor therapy.

many acute infarcts occur without associated acute arterial obstruction.[10] We do not know to what extent this state of affairs may apply to acute cerebral damage.

BLOOD PRESSURE RESPONSE FOLLOWING COMBINED ADRENALECTOMY AND SYMPATHECTOMY

Data bearing upon blood pressure responses to operation are shown in Table IV. The classification of responses as A, B, C and D is admittedly arbitrary and open to criticism. For example, in some patients, systolic and diastolic pressures did not both fall within the limits set for each group which sometimes led to assignment to a less favorable group than the mean pressure might have warranted. Moreover, many of the patients who by this method of classification had to be placed in Groups C and D had actually exhibited as much reduction in pressure from preoperative levels as those in Groups A and B. Furthermore, the extent of postural hypotension after operation is ignored in this classification. Nevertheless, it was thought preferable to classify the results in relation to a normal pressure

rather than with respect to the fall from preoperative levels. The blood pressure figures employed in Table IV represent averages of readings made during the past year. It is to be noted that the classifications have been made irrespective of the employment of vasodepressor therapy and that four of the 48 cases in Group A and five of the 27 in Group B receive at least some drug treatment which may help to maintain them in these categories.

The table does not show separately the blood pressure responses following total versus subtotal adrenalectomy, no superiority of one procedure over the other having been demonstrated. The blood pressure responses tabulated with respect to the Smithwick classification show that in Group IV, despite the relatively high mortality since operation, 23 of the 40 surviving patients have exhibited either an A or B response. The falls in blood pressure noted in patients submitted to adrenalectomy have tended to be permanent in contrast with the gradual rise toward the preoperative level often observed after sympathectomy alone. Indeed, in some, further lowering of pressure has occurred as the number of years after operation has increased.

After fairly frequent experiences in the early part of the study with minor grades of adrenal deficiency, it seemed preferable to carry the patients along on more liberal replacement to avoid such episodes. This has undoubtedly resulted in at least slightly higher blood pressure levels in some, than if they had been managed close to the borderline of adrenal insufficiency. However, it must be emphasized that although there are very few patients in whom arterial blood pressure can not be reduced at least to some degree by combined adrenalectomy and sympathectomy with at least enough benefits in those who survive to justify the operation, the blood pressure with the patient in the supine position remains at undesirably high levels in about 25 to 30 per cent. In some of these, the high pressure persists, despite what appears to be adequate renal function, even when they are permitted to lapse temporarily into a state of adrenal deficiency.

Changes in Eyegrounds

Among the 114 survivors of combined adrenalectomy and sympathectomy, 17 were classified prior to operation by members of the Ophthalmology Staff as exhibiting Grade 4 hypertensive retinopathy

because the findings included swelling of the discs, and 36 with Grade 3 changes because of hemorrhages or exudates or both. Fifty-seven were classified as exhibiting Grade 2 vascular changes and four, Grade 1 changes. Among 80 of the same patients re-examined during the past year, none were found to show Grade 4 changes; four, Grade 3; 48, Grade 2 and 28, Grade 1 changes. Reports made prior to one year ago or by other examiners are not included here. When swelling of the disc was present it diminished within a few days after the completion of the operation, disappeared quickly in every patient and, so far as we are aware, has never recurred in any. The four cases which remain in Grade 3 were so classified because they exhibited an occasional hemorrhage. Improvement in the appearance of the vessels has been a slow process save for diminution of attenuation but over the course of several years has led to marked increase of the number placed in the Group I category. Improvement in funduscopic findings has been observed after sympathectomy alone even in cases in which little reduction of blood pressure during recumbency has occurred. Improvement has also been reported frequently during the past few years following drug therapy of hypertension. We are unable to determine the contribution of adrenalectomy to the results presented here although we have never observed the rapid reduction in swelling of the disc following any other method of treating hypertension.

Cardiac Effects. The Electrocardiogram, Heart Size, Congestive Failure and the Anginal Syndrome

Among 114 survivors of the combined adrenalectomy and sympathectomy operation, electrocardiograms have been obtained during the past year in 92. Fifteen of these patients exhibited a normal electrocardiogram both before and after operation. In 55, there was "improvement" during the follow-up period. In 17, the findings remain essentially unchanged. Five are regarded as "worse", two because of myocardial infarction; one, right bundle branch block; one, bigeminal rhythm, but only one because of increase in the changes originally attributed to the hypertensive state.

In the same group of patients, orthodiagrams or x-ray films were obtained in 92 during the past year. Of 65 with an enlarged heart before operation the heart size decreased in 38, remained the same in

25 and increased in two. In 27, the heart was not enlarged before or after operation.

Among the patients subjected to adrenalectomy alone during the early part of this study, there were two patients in whom, prior to operation, congestive failure could not be brought completely under control. In addition, the patient who several years before subtotal adrenalectomy had undergone a Peet thoracic sympathectomy, developed recurrent bouts of pulmonary edema while under treatment in the hospital. Unexpectedly prompt relief of cardiac failure occurred in these three patients following adrenalectomy. Forty-four of the 114 survivors of combined adrenalectomy and sympathectomy were classified as exhibiting evidences of heart failure prior to operation, although in only 20 was failure regarded as sufficiently advanced for maintenance on digitalis. There is no recent report in seven of these patients but only three of the remaining 37 are now regarded as having even minor evidences of failure and only three receive digitalis, one because of atrial fibrillation. The relief from congestive heart failure after adrenalectomy does not appear to depend to any great extent upon reduction of blood pressure, because in several of our patients, rapid complete relief appeared before much fall in pressure occurred. The observations of Thorn and his co-workers[8] following total adrenalectomy suggest that increase in sodium excretion helps to relieve congestive failure. This view is supported in studies made by Hills, Zintel and Parsons[11] in some of our patients. Even those patients who under ordinary circumstances required no replacement therapy, lost sodium on a low sodium intake.

Twenty-three of the 114 survivors were subject to the anginal syndrome before operation. Twenty of these now suffer less anginal pain or have none at all. Only one patient is known to have developed exertional anginal seizures several years after operation despite completely normal blood pressure during that period. Nevertheless, the fact that 11 of the 40 deaths subsequent to the same operation resulted from coronary disease demonstrates that it remains a serious problem after adrenalectomy and sympathectomy.

Renal Function

Although the BUN was determined in all patients prior to operation, it became a less reliable index of renal function after adrenal-

ectomy, its levels being influenced by the status of adrenal cortical function at the time of the test. For this reason we have utilized the excretion of PSP during the first 15 minutes after intravenous injection as our postoperative standard test of renal function. Because of the importance of accurate technique in this test, we have accepted the results of tests made only under supervision in the hospital wards or in the Adrenalectomy Follow-Up Clinic. All patients had received the PSP test prior to operation. Fifty-eight of the 114 survivors of the combined operation have been retested during the past year. In 16, the results were essentially the same as before operation, in 21, slightly better and in 21 slightly worse. From these results and those obtained in other patients in preceding years, it is concluded that in hypertensive patients who undergo this operation, renal function tends to remain practically stationary. We have already pointed out that only one patient died of uremia beyond the first year after operation. Four patients in whom the PSP excretion prior to operation was less than 15 per cent in the first 15 minutes have escaped further serious renal deterioration.

Headache, Tension and Hypertensive Encephalopathy

Headache had been reported prior to operation in 70 of the 114 survivors of combined adrenalectomy and sympathectomy. In 62, the headache was relieved or disappeared entirely after operation, in three, it was unimproved and in five there are no recent reports. It is not certain that all headaches in these patients were related to their hypertension. Becauses similar results have been observed after sympathectomy alone, we are unable to estimate the contribution of adrenalectomy to the results reported here. However, relief of headache occurred in some of the patients in whom adrenalectomy alone was performed.

The second patient submitted to adrenalectomy alone, a woman known to one of us since her childhood, who had extremely high blood pressure, slight motor residua from a stroke and blindness of one eye from occlusion of the central artery of the retina, volunteered the statement ten days after operation that she no longer noted the emotional tension that she had regarded as one of her most troublesome symptoms ever since she had developed arterial hypertension many years before. At the time she stated that tension was relieved

she knew that there had been little reduction in the arterial pressure from the preoperative level. She has had no recurrence of tension in the six and a half years since operation. A few other patients have volunteered similar statements regarding the relief of tension after operation and in many others a similar history could be elicited by questioning. The time relation of relief of emotional tension to adrenalectomy suggests that it is brought about by deprivation of some adrenal hormonal effect, either medullary or cortical.

The type of hypertensive encephalopathy characterized by impairment of mental faculties at times approaching stupor, usually in association with severe headache and marked choking of the discs, was present in two of our patients prior to operation. Although relief of headache occurred promptly after operation, recovery of mental acuity was a much slower process. One, who has no memory of his hospital stay was able to resume his work as a public utility supervisor six months after operation. The other, after having made a good recovery from a similarly severe state died more than a year later from an acute cerebral vascular accident.

Skin Pigmentation

The pigmentation of Addison's disease has appeared in 36 of the 118 survivors of adrenalectomy,* although in most it has been slight in contrast with the marked pigmentation so frequently encountered in spontaneous Addison's disease. It may occur after total or subtotal adrenalectomy apparently with equal facility, including those patients with enough preservation of adrenal function which under ordinary circumstances requires no replacement therapy. In this series, pigmentation developed within the first few months after operation or not at all. It could sometimes be lightened but not abolished by larger dosages of cortisone than were necessary for replacement therapy. These data obviously support the impression derived from the study of spontaneous Addison's disease that pigmentation is in some way related to deficiency in adrenal cortical function. But the process by which pigmentation develops remains obscure, as does the reason why pigmentation tends to be deeper as well as more frequently present in spontaneous Addison's disease than in iatrogenic cortical deficiency.

* The cases cited by Hills, Zintel and Parsons[11] in their discussion of "melanosis" are part of this group.

Raynaud's Phenomenon

Relatively mild grades of Raynaud's phenomenon occurred in 19 patients to the degree that it caused "dead fingers" upon exposure to cold. No treatment beyond the use of loose fitting warm gloves when going out into the cold seemed necessary.

Peptic Ulcer

The occurrence of recognized peptic ulcer in eight cases and death from that cause in one patient and possibly another was a cause for concern. To what degree sympathectomy, adrenal deficiency and replacement therapy each contributed to this unfortunate complication has not yet been established. In patients who had received Rauwolfia drugs, this form of therapy must also fall under suspicion.

Adrenal Insufficiency in Relation to Blood Pressure Levels and its Management Following Adrenalectomy for Hypertension

In two patients among the earliest operated upon, 10 per cent or more of adrenal tissue was left in situ. Neither adrenal cortical deficiency nor significant reduction in blood pressure ensued. Because this blood pressure behavior contrasted so unfavorably with that of our first patient referred to above in whom approximately 5 per cent of adrenal tissue had been left in situ, no further effort was made to test the effects of less radical adrenalectomy. But in subsequent cases when the blood pressure response was less than satisfactory and no signs of adrenal deficiency appeared, we had to question whether enough adrenal tissue had been removed to obtain the maximum possible benefit. It was therefore decided to attempt to test the relative merits of total adrenalectomy versus the subtotal procedure, both carried out in conjunction with sympathectomy. Hills, Zintel and Parsons[11] found evidence suggesting slight adrenal regeneration in only one of our patients who had been subjected to subtotal adrenalectomy. However, almost as much replacement therapy was still required in this patient three years after operation as in previous years. In eight of 27 patients with subtotal adrenalectomy, no exogenous hormone was required. Four, however, had minimal requirements comparable to the mean minimal requirement of totally adrenalectomized patients, which in a group of 17 was 32.7 mg. of cortisone and 1.7 mg. of

buccal DCA. In the subtotally adrenalectomized patients, including those without need for replacement therapy, the mean minimum requirement was 12.4 mg. of cortisone and 0.7 mg. buccal DCA, values which are close to the mean minimum requirement noted in nine cases of spontaneous Addison's disease. Among the totally adrenalectomized patients, one who received no replacement therapy for five weeks, exhibited no clinical adrenal deficiency during that period. It is inferred that in this patient, accessory adrenal cortical type tissue was capable of supplying minimal cortical hormone requirements.

It now seems likely that adrenal regeneration will not interfere seriously with results achieved by subtotal adrenalectomy. In fact, save in the one patient mentioned above, minimum replacement requirements became stabilized within six months following operation and have not changed over the course of years. In approximately one-fourth of the patients, the amount of adrenal tissue which survives after an estimated 5 per cent is left in situ, is capable of maintaining a satisfactory state of health in the absence of acute infection, vomiting or diarrhea. Accessory adrenal cortical function appears to be a rare finding and of little practical importance.

The large dosages of cortisone employed to maintain patients after total adrenalectomy for metastatic malignancy[12] are often inappropriate for patients in whom the purpose of adrenalectomy is control of hypertensive disease. Cortisone can sometimes be employed in large dosage for short periods of time in previously hypertensive patients without objectionable vasopressor effects. In general, however, it seemed advisable, because of vascular reactivity to unnecessarily large dosages, to determine the minimum amount of replacement therapy required to avoid clinical adrenal deficiency and disturbances in blood electrolyte levels and then adhere closely to such dosages. Under these circumstances, many of the patients have required supplements of DCA and liberal salt intake, the latter especially in hot weather. Such a method of treatment has required closer observation of patients than when their hormonal requirements can be exceeded by a wide margin. To what extent the grades of renal damage which persist in those who had been subject to severe hypertensive disease, contribute to the effects of excessive amounts of hormones in elevating blood pressure, is not clear at this time. Cortisone, especially when given in excess of the actual need, has sometimes stimulated the appetite in our patients

with consequent undesirable gain in weight. Recently 9-alpha-fluorohydro cortisone in dosage of 0.1 mg. daily has been substituted for DCA and salt. This has permitted slight reductions in dosages of cortisone. Whether or not the tendency to obesity will be lessened by this change in treatment remains to be determined.

Discussion

Evaluation of treatment of hypertensive disease must take into account significant characteristics of the disorder among which the following appear most important: 1) The course of events in many patients is subject to unexpected turns for the better or worse, the causes of which often remain obscure. 2) Blood pressure levels recorded by the examiner are not necessarily a reliable index of the severity of the disorder because of (a) variability in the neurogenic response of the patient to the test itself and (b) the probability that some individuals tolerate the influence of high blood pressure upon blood vessels and vital organs better than others. 3) The pathologic consequences of hypertension although they tend toward progression when the blood pressure remains high, are apt to advance in an irregular fashion. 4) There is a lack of homogeneity in the material because the total clinical pictures differ so widely, a matter which must be taken into account in attempting to apply statistical analysis to the results of treatment.

Smithwick has attempted to circumvent the lack of homogeneity by his method of grading hypertensive disease. It is not necessarily the best possible method of grading and appears to be open to criticism because it fails to take into account the rate of progression of the disorder and its attendant pathologic lesions, but it has proven useful. Thus Smithwick has demonstrated that the rate of mortality following thoracolumbar sympathectomy is progressively higher in his Groups II, III and IV. In fact he appears to have concluded that thoracolumbar sympathectomy should not be carried out in patients in whom the disease has progressed to Grade IV status.[13] This last group is the one in which we have had special interest. The pathologic lesions in this group are usually already well advanced. When spontaneous improvement occurs it is apt to be limited in degree and temporary, similar to the improvement frequently noted after diverse types of major surgical operations. Long term reduction in blood pressure to

normal levels or its vicinity without treatment is rare save as a result of myocardial infarction or occasionally following a cerebral vascular accident. The mortality rate following combined adrenalectomy and sympathectomy in this group has been comparatively high although accounted for in part by the large number of "desperation" cases included which would have fallen in Smithwick's discarded Group V. Although 25 of the 65 patients in our Group IV are now dead, most of the remainder have been to a considerable degree rehabilitated. In fact, most of the patients in this group who died a year or more postoperatively as a result of acute vascular episodes, had been markedly improved up to the time these episodes occurred.

There can be little doubt that the incidence of causes of death in hypertensive disease has been greatly altered by adrenalectomy and sympathectomy as is demonstrated by no deaths from congestive heart failure, the fact that deaths resulting from cerebral vascular seizures exceeded deaths from coronary obstruction by a wide margin and that only one death from uremia occurred after postoperative survival for one year. It is noteworthy that 29 of the 40 deaths resulted from acute episodes of vascular obstruction, 18 of which were cerebral.

One of the most striking phenomena observed in this study has been the wide range in the effects of adrenalectomy upon blood pressure levels. It is now well known that patterns of urinary excretion of adrenal steroid metabolites exhibit individual differences. But, so far as we are aware, nothing has been discovered in urinary excretion studies which would point toward alteration in adrenal cortical secretion in patients with essential hypertension and nothing which would enable one to predict the effect of adrenalectomy upon elevated blood pressure. Pathological studies of the adrenal glands removed from our hypertensive patients have exhibited no abnormality that would differentiate them from the adrenal glands of patients with normal blood pressure. Whether the variability in blood pressure response following adrenalectomy in hypertensive patients which can not now be accounted for (save for the failures caused by advanced renal disease) is due mainly to unrecognized differences in patterns of adrenal secretion or to differences in the influence of normal adrenal secretion upon other parts of the mechanism concerned in blood pressure regulation is a problem, the answer to which should throw some light upon the mystery of essential hypertension. The probability now seems to be

that the adrenal glands are not at fault in that disorder. But it would be of great practical value to be able to predict the blood pressure response of hypertensives to adrenalectomy. In our experience at least half the patients with severe hypertensive disease subjected to combined adrenalectomy and sympathectomy exhibit a total improvement, i.e., in symptoms, regression in abnormal findings and rehabilitation to a degree that in our experience is exceptional following other methods of treatment including the newer combinations of vasodepressor drugs. Nevertheless we believe that the indications for this operation and contraindications developed in this study should be followed unless or until the blood pressure response can be predicted with a close approach to accuracy. Such an achievement would justify broadening of the scope of the operation to many of the patients now carried along on vasodepressor drugs with mediocre results.

Summary

In an exploratory study of operative procedures for the control of hypertensive disease refractory to other methods of treatment, subtotal adrenalectomy alone (13 patients) and subtotal or total adrenalectomy in combination with abdominal or thoracolumbar sympathectomy (155 patients) have been carried out.

The contraindications to these operations which became evident during the course of the study are stated.

The number of deaths and their causes both during the immediate postoperative period and subsequent to recovery from operation are presented and discussed. Changes from the usual incidence of causes of death in hypertensives are pointed out.

The amount of adrenal tissue which survived after approximately 5 per cent was left in situ, has been adequate in about one-fourth of the patients to maintain them in a state of health without clinical adrenal insufficiency unless acute infection, vomiting or diarrhea occurred. In a few patients, no evidence of adrenal function remained. In the majority, replacement therapy was needed but the minimal hormonal requirement was less than in totally adrenalectomized patients.

Adrenal function following recovery from subtotal adrenalectomy has remained stable for periods up to six years. Slight reduction in minimal hormonal requirements has been observed in only one patient.

Accessory adrenal cortical function, adequate to supply minimal hormonal requirements, is inferred to have been present in only one patient after total adrenalectomy.

Combined adrenalectomy and sympathectomy have been preferred to adrenalectomy alone because of prompt fall in blood pressure and the long persistence of a postural fall in pressure after completion of the combined operation. Subtotal and total adrenalectomy in the combined operations appear to have been equally effective in helping to reduce the blood pressure.

The results of the combined operations upon blood pressure, headache, funduscopic findings, anginal pain, congestive heart failure, heart size, electrocardiogram and renal function and the incidence of pigmentation, peptic ulcer and Raynaud's phenomenon are presented.

The total effects of combined adrenalectomy and sympathectomy, i.e., upon the blood pressure, symptoms, physical findings and degree of rehabilitation of severe hypertensives refractory to other methods of treatment, although beneficial to some extent in nearly all survivors, have been highly favorable in about one-half the patients operated upon. These favorable results in our experience are rarely equalled over extended periods by drug antihypertensive therapy in similarly severe situations even in the patients who appear to respond best to drug therapy.

No successful procedure has thus far been devised for selecting patients capable of a highly favorable response to adrenalectomy and sympathectomy. Such a development would greatly extend the sphere of usefulness of the combined operations employed in this study. At present, however, it appears that such operations should be limited to those with an urgent need for control of their hypertensive disease but who respond poorly to antihypertensive drugs or are unable to tolerate them.

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HYPOPHYSECTOMY IN UNSTABLE DIABETICS WITH PROGRESSIVE RETINAL AND RENAL VASCULAR DISEASE*

LAURANCE W. KINSELL
Director
Institute for Metabolic Research of Higland-Alameda County Hospital, Oakland, California

DURING the period December 1953 to November 1955, nine hypophysectomies have been carried out in diabetics who have been temporarily or constantly under our care. All of these patients have been unstable juvenile diabetics. All have had evidence of progressive vascular disease involving the eyes and kidneys. Of these patients, three are living. In the others death resulted from progressive renal insufficiency, in one patient associated with acute coronary occlusion, and in another with acute pneumonitis.

Of the three who are living, one was operated upon in September 1954, one in November 1954 and the third in November 1955. There has been no operative mortality. As previously reported,[1] the first two patients who had very far advanced renal disease died within approximately three months. Survival of the others averaged about one year. The patient who was operated upon in November 1955 has a functionally incomplete hypophysectomy. His diabetes has been somewhat less unstable, although his insulin requirement has diminished very little. During the past six months he has had little or no evidence of progressive retinal vascular disease.

Of the two patients whose survival exceeds two years and whose hypophysectomy is functionally complete, the following observations apply:

1. Diabetes was first manifested in these patients in childhood; diabetic control was poor; and obvious eye involvement appeared between 15 and 20 years after the known onset of the disease.

2. Average maintenance hormonal therapy is: NPH insulin less than 15 units daily; cortisone or hydrocortisone acetate less than 15 milligrams daily; tri-iodo-thyronine 25 micrograms daily; testosterone cyclo-

* Presented at The New York Academy of Medicine, October 15, 1956, at its 29th Annual Graduate Fortnight.

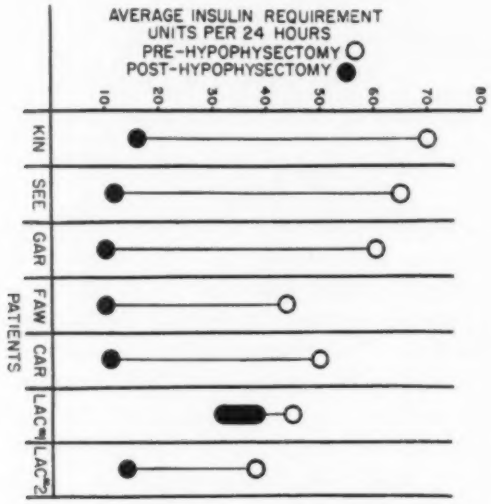

Figure 1—Change in insulin requirement as the result of hypophysectomy.

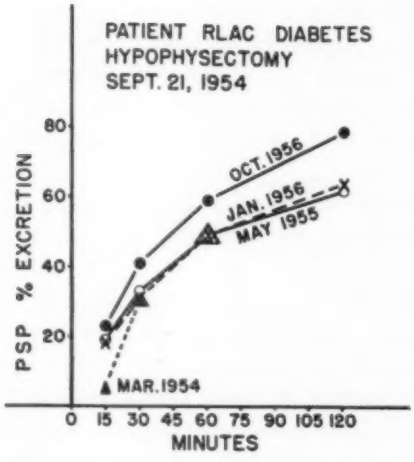

Figure 2—Renal function in surviving patient RLAC.

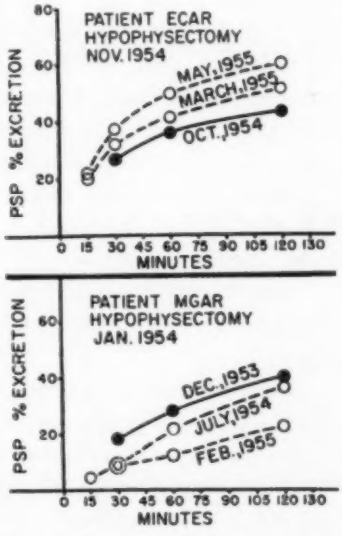

Figure 3—Renal function studies in patients MGAR (deceased) and ECAR (Surviving).

pentyl propionate 200 milligrams every two to four weeks. (All of our survivors are males.) Anabolic steroid therapy in females consisted of ethinyl estradiol 0.05 milligrams daily (or its equivalent); testosterone cyclopentyl propionate 2.5 to 5 milligrams every two weeks. In Figure 1 are shown the pre- and post-hypophysectomy insulin requirements in the first six patients. (Patient LAC required re-operation because of evidence of incomplete hypophysectomy.)

3. Each patient has a greater amount of useful vision than was the case prior to surgery. Patient CAR still experiences small retinal hemorrhages. Dr. Dudley Bell examined patient LAC on October 11, 1956 and reported he had "94 per cent normal vision with correction" in his one eye. (The other eye was removed because of glaucoma, secondary to extensive hemorrhage.) He found minimal exudate and no evidence of hemorrhage.

4. Each patient has at least "held the line" in regard to renal efficiency. In Figures 2 and 3 are shown serial PSP excretion figures in these two patients, RLAC and ECRA; and also (for contrast) the PSP figures in patient MGAR who was hypophysectomized in January of 1954 and who died (of renal failure) in May 1955.

Discussion

Progressive vascular disease in the diabetic, with particular reference to the juvenile diabetic, is one of the great challenges in clinical medicine.

That an adequate answer exists in terms of prevention is beyond question. That this answer still eludes us is equally beyond question. Factors which must be considered include heredity, exercise, diet, hormones and relative or absolute adequacy of diabetic control. That poor diabetic control bears a statistical relationship to early onset and rapid progression of vascular disease appears to be established beyond reasonable question. That some patients who have good diabetic control develop progressive vascular disease is, unfortunately, also unquestionable.

As noted in our original report we felt certain that hypophysectomy would transform an unstable diabetic with a relatively high insulin requirement to a mild diabetic with a low insulin requirement, and that hypertension would be ameliorated. Both of these expectations have been fulfilled. That the majority of our patients with well established renal disease have progressed to a fatal outcome despite hypophysec-

tomy is obvious. Whether hypophysectomy has slowed the progression of retinal and renal vascular disease in the surviving patients, we do not know. In evaluating any therapeutic procedure designed to favorably modify this type of vascular disease, one must use as his yardstick the knowledge that many such individuals will have sudden remissions (and exacerbations) in their vascular disease for completely unknown reasons.

At the present time we are engaged in the evaluation of a steroid preparation (17-ethyl-19-nortestosterone). In some unstable juvenile diabetics this produces impressive stabilization, frequently in association with diminished insulin requirement. Other steroid preparations also are under constant evaluation. The progression of the vascular disease in such individuals as compared with that in our hypophysectomized diabetics, is so far impossible of evaluation in meaningful fashion. In view of the unavoidable hazard associated with hypophysectomy, and the extremely questionable benefits, it is our present feeling that such surgery should be resorted to, if at all, only in individuals who manifest progressive vascular disease despite any and all other therapeutic procedures. Such individuals must be emotionally stable, and should have a reasonable renal reserve. In a clinical sense we would define "reasonable" renal reserve as the ability to maintain a normal blood urea nitrogen during the intake of a diet which contains 75 grams of protein, and which is nutritionally adequate in all other respects.

In conclusion it is our strong belief that the most important weapon presently available in the prevention of diabetic vascular disease is the proper handling of the newly discovered juvenile diabetic. A unit approach is essential. If the unit functions efficiently, one will have a diabetic child with a deep fund of equanimity; and, we suspect, a child who will never develop brittle diabetes. Such a patient will readily take in his stride the "nuisance factors" associated with the maintenance of constancy and adequacy of (a) exercise (b) diet and (c) insulin.

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INTESTINAL OBSTRUCTION IN THE NEWBORN*

THOMAS V. SANTULLI

Assistant Professor of Clinical Surgery,
College of Physicians and Surgeons, Columbia University

THE problem of intestinal obstruction in the newborn period, i.e., in the first 30 days of life, still presents a great challenge to both the pediatrician and the surgeon. Although a great deal has been accomplished in the treatment of obstruction in recent years, the mortality of this condition in the newborn infant would still appear to be inordinately high. We have reported our experiences previously[1] in an attempt to analyze critically the problem of diagnosis, the factors which affect the prognosis; the causes of death and the follow-up results in this age group.

The present report is based on 207 consecutive cases of neonatal obstruction that were seen at Babies Hospital, New York City, from 1939 through 1955. In each case the diagnosis was confirmed at operation or at autopsy. The study includes cases of obstruction of the small intestine and colon. It does not include obstructions of the esophagus, stomach and rectum. Neonatal obstructions of the rectum have been reported elsewhere.[2]

This presentation gives a brief account of these 207 cases. Comprehensive discussions of the various conditions can be found in the reports of many authors.[3-22] Emphasis will be given to the factors affecting the prognosis, the causes of death and the follow-up results. Because of the recent pediatric and surgical interest in meconium ileus and congenital megacolon in the newborn period, special attention will be given to these conditions.

DIAGNOSIS

It has often been said that "to treat an infant as a small edition of an adult is to invite disaster." This admonition is certainly borne out

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From The Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Surgical Service of the Babies Hospital.

in the subject under consideration. Although the significance of such symptoms as vomiting and abdominal distention have the same importance in the adult as in the newborn infant in directing the physician's attention to obstruction, it must be emphasized that the infant has a small reserve in any acute illness and that the physiologic disturbances associated with obstruction are much more acute and often fulminating in this age group.[23,24] Hence, early diagnosis is of paramount significance and actually becomes the most important single factor in the prognosis.

Early diagnosis is merely a matter of acute awareness of the problem in the newborn period. Many lives could be saved if one followed the simple dictum that any newborn who vomits, especially if he vomits bile, or shows abdominal distention, is suspect and deserves plain 3-position x-rays of the abdomen without delay. The diagnosis is especially treacherous in the premature infant who may show very little or no clinical evidence of peritoneal reaction even in the presence of a closed loop obstruction or peritonitis. It is easy to err on both sides in the premature infant, i.e., missing the diagnosis of obstruction or operating in the absence of actual obstruction. Certainly, the most important single diagnostic measure is the plain x-ray using the conventional 3 positions. Rarely, is contrast medium needed and, indeed, it should be avoided in the usual case.

Etiology

An outline of the causes of obstruction which we find useful in classifying our lesions is shown in Table I. Tables II and III present the frequency of the various lesions, the results and follow-up data of the present series. It should be emphasized that the material includes only those cases of obstruction which were admitted to the Babies Hospital in the newborn period.

Atresia and Stenosis

These intrinsic obstructions comprised over one-quarter of the total. This distribution of the lesions and results are shown in Table IV. Atresia and stenosis of the colon, exclusive of the rectum, are rare. More than one site of atresia was found in five of 38 cases. In two of these, there were 12 points of atresia. This corresponds to the incidence of 15 per cent of multiple atresias reported by others.[25]

TABLE I.—CAUSES OF INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT

I. *Mechanical*
- A. Congenital
  - 1. Intrinsic
    - a. Atresia and stenosis
    - b. Meconium ileus
    - c. Hypertrophic pyloric stenosis
    - d. Meconium "plug"
  - 2. Extrinsic
    - a. Malrotation with or without midgut volvulus
    - b. Volvulus without malrotation (local volvulus)
    - c. Congenital peritoneal bands
    - d. Incarcerated hernia- inguinal, internal, diaphragmatic
    - e. Annular pancreas
- B. Acquired
  - 1. Intussusception
  - 2. Peritoneal adhesions
    - a. Following surgery
    - b. Following peritonitis

II. *Neurogenic*
- A. Defective intrinsic innervation (aganglionosis)
  - 1. Colon and rectum—congenital megacolon
  - 2. Small intestine
- B. Paralytic ileus
  - 1. Cerebral injury
  - 2. Infection

Causes of the high mortality are discussed later. The follow-up period for the 24 survivors has been three months to 9⅓ years. In 21, the follow-up data is complete (followed to the present time). In two, the follow-up was incomplete but adequate. These were operated upon 11 and six years ago and were last seen six and 3½ years later, respectively. One patient who had an excellent result one year following her operation 13 years ago, has not been seen since.

The youngest survivor, now three months old, required a tracheostomy because of postoperative laryngeal obstruction but is in excellent condition. Another patient had three operations because of breakdown of the anastomosis but is now well 16 months following the

TABLE II.—INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT (BABIES HOSPITAL 1939-1955)

Cause	*No. of Cases*	*Recovered*	*Died*	*Mortality (%)*
Atresia and stenosis	57	24	33	58
Meconium ileus	37	12	25	67.5
Malrotation	30	25	5	16.6
Aganglionosis	28	20	8	28.8
Inguinal hernia	14	14	0	
Congenital peritoneal bands	12	8	4	
Local volvulus	10	5	5	
Adhesions, postoperative	2	2	0	
meconium peritonitis (cause undetermined)	6	2	4	
Internal hernia	3	2	1	
Intussusception	3	1	2	
Annular pancreas	1	1	0	
Meconium "plug"	1	1	0	
Multiple causes	3	3	0	
TOTAL	207	120	87	42

TABLE III.—STUDY OF 207 CASES

Deaths			87
Autopsies done in	81		
Recoveries			120
Lost to Follow-Up	8	(6.6%)	
Adequate Follow-Up	112	(93.4%)	
Complete Follow-Up (to date of present report)	96	(80%)	

last operation. A third patient died four months later from surgery related to a neuroblastoma but had been relieved of a duodenal obstruction in the first week of life. All of the others are in excellent condition, without symptoms referable to their lesion or to the surgery.

TABLE IV.—ATRESIA AND STENOSIS

Site	*No.*	*Recoveries*	*Deaths*
Atresia			
Duodenum	11	5	6
Jejunum	5	1	4
Ileum	16	7	9
Colon	1	1	0
Multiple	5	0	5
TOTAL	38	14	24 (63%)
Stenosis			
Duodenum	10	6	4
Jejunum	2	0	2
Ileum	5	3	2
Colon	2	1	1
TOTAL	19	10	9 (47%)
Total number of atresia and stenosis	57	24	33 (58%)

MALROTATION

In this group of 207 cases of intestinal obstruction in the newborn infant only 30 were due to malrotation. Although many other cases were seen after this thirty-day period, they are not included in this study.

Anomalies of rotation gave rise to intestinal obstruction in two ways in this small series:

1. Most commonly the obstruction was due to volvulus of the midgut loop. This portion of intestine includes the jejunum, ileum, and large intestine up to the middle of the transverse colon, i.e., the segment supplied by the superior mesenteric artery. Failure of fixation of the mesentery, the short primitive duodenocolic isthmus, and the narrow pedicle of the mesentery allow the entire midgut loop to twist around its limited attachment resulting in obstruction of the duodenum. It occurred in 27 of our 30 cases (Table V). The volvulus was always in the clockwise direction and torsions of 180 degrees to four complete turns were seen. The tightness of the volvulus rather than the number of turns determined the severity of the symptoms.

TABLE V.—MALROTATION WITH NEONATAL OBSTRUCTION

Number of Cases		30
With volvulus of midgut	27	
Without volvulus	3	
With associated peritoneal bands	16	
Cases with gangrene	5	
OPERATIVE PROCEDURES		
Number of Cases		30
Reduction with cecopexy	13	
Reduction with division of peritoneal bands (Ladd's operation)	12	
Division of peritoneal bands (no volvulus)	3	
Resection and anastomosis	2	
Recurrence of volvulus	1	
Deaths	5	(16.6%)

The picture was usually that of incomplete duodenal obstruction with intermittent vomiting of copious amounts of bile-stained fluid.

Since the superior mesenteric vessels form the pedicle around which the volvulus occurs, there may be obstruction of the vascular supply to the intestine. The symptoms and signs of strangulation obstruction ("blue-bowel syndrome") are then added to those of simple obstruction. In some cases, the passage of blood by rectum was the first sign. With complete occlusion of the vessels, gangrene of the entire midgut may occur. This was seen in three of our cases. In two patients, gangrene of a limited segment of intestine occurred and resection was possible.

2. Less frequently, the obstruction was due to incomplete rotation of the cecum, without volvulus of the midgut. This was found in three cases (Table V). The cecum lies in the upper abdomen and there are congenital peritoneal bands associated with this malposition. These broad bands course from the cecum or the transverse colon over the descending part of the duodenum and are attached to the undersurface of the liver or to the posterior abdominal wall in the right upper quadrant of the abdomen giving rise to partial duodenal obstruction. Sometimes the obstruction is due to pressure from the overlying cecum itself.

Reduction with cecopexy (attaching the cecum in the right lower quadrant of the abdomen) was done in 13 cases. This procedure has always been strongly advocated by Donovan[26] as a safeguard against recurrent volvulus since it gives a wider base of attachment to the midgut segment. Ladd's procedure of dividing all of the congenital peritoneal bands thereby freeing the duodenum and allowing the cecum to lie in the left side of the abdomen was carried out in 12 of the cases.

The follow-up period for the 25 survivors was two months to 12 years. Five of the patients required operation for intestinal obstruction due to postoperative adhesions.

The follow-up is complete in 23 of the cases. They are asymptomatic. Two of the patients who were operated upon 15 and 16 years ago were free of symptoms when last seen eighteen months and two months respectively after operation.

Meconium Ileus

According to the recent studies of di Sant'Agnese[27] about 10 per cent of patients with fibrocystic disease of the pancreas seen at the Babies Hospital also presented intestinal obstruction in the newborn period. The ileus is due to an abnormal meconium which becomes inspissated in the lower ileum and blocks the lumen of the intestine. This is considered to be the earliest and severest manifestation of a generalized disease which is hereditary and in which probably all of the exocrine glands are affected.

The characteristic picture is one of hypertrophy and dilatation of the mid-ileum which contains semi-fluid and tenacious meconium. The distal 10 to 20 cm. of ileum are filled with hard, gray concretions resembling dry putty. The large intestine is usually empty, small and hypoplastic.

In 1938 Andersen[28] recorded the first complete description of the disease and noted the association of meconium ileus with cystic fibrosis of the pancreas. In 1944 Farber[29] related the deficient pancreatic enzymes to the abnormal meconium. In 1942 Hurwitt and Arnheim[30] reviewed the literature and were unable to find any instance of recovery. In 1948 Hiatt and Wilson,[31] of this institution, described a new method of treatment and reported the first successfully treated cases. In 1952 Gross[4] reported on a remarkable series of 19 cases treated by a Mikulicz type of resection and double ileostomy with

TABLE VI.—MECONIUM ILEUS PREOPERATIVE DIAGNOSIS

Meconium ileus	15
Atresia of intestine	11
Volvulus	4
Intussusception	1
Intestinal obstruction-? cause	6
	37

TABLE VII.—MECONIUM ILEUS ASSOCIATED PATHOLOGY

Total Number of Cases		37
Cases with Associated Intestinal Pathology		23*
Volvulus of small intestine	16	
Congenital peritoneal bands	4	
Malrotation	3	
Meconium peritonitis (3 with "cyst" of intestine)	7	

* More than one lesion in some cases

TABLE VIII.—MECONIUM ILEUS RESULTS OF SURGICAL TREATMENT

Type of Operation	*Cases*	*Operative Deaths*	*Relieved of obstruction*
Removal of meconium through ileotomy	10	7	3
Removal of meconium through ileotomy, reduction of volvulus	6	2	4
Removal of meconium, resection of volvulus, anastomosis	4	1	3
Removal of meconium through ileotomy, ileo-colostomy	1	1	0
Double ileostomy (Mikulicz)	3	3	0
Resection of volvulus, double ileostomy	4	4	0
Resection of volvulus, anastomosis	1	1	0
Reduction of volvulus (only)	2	2	0
Ileo-colostomy (only)	2	2	0
Manipulation of intestine	2	1	1
Division of peritoneal bands	2	1	1
TOTAL	37	25	12

TABLE IX.—SUMMARY OF RESULTS—MECONIUM ILEUS

Total (Surgery for neonatal obstruction, Babies Hospital 1939-1955)		37
Operative Deaths	25	
Relieved of obstruction by operation	12 (32%)	
*Died later of:		
pulmonary infection	7	
malnutrition and dehydration	1	
Living (January 1956)	4 (11%)	

* 3 in first year, 2 in third year, 2 in fourth year, 1 in ninth year

TABLE X.—MECONIUM ILEUS SURVIVORS (JANUARY 1956)

Patient	*Year*	*Operation*	*Maximal Follow-Up*	*Follow-Up*	*Recent X-Ray Chest*
J.M.	1947	Ileotomy, removal meconium	8½ Yrs.	Admitted B.H. at 6 yrs. for Fever ? cause 8 Years—Excellent	normal
P.M.	1953	Resection volvulus, removal meconium, anastomosis	2¾ Yrs.	Admitted B.H. at 1 yr. for Inguinal hernia 2¾ Years—Excellent	normal
M.D.	1953	Reduction volvulus, removal meconium	2¾ Yrs.	Admitted B.H. at 9 Mos. for Inguinal hernia 2½ Years—Excellent	normal
C.C.	1953	Resection volvulus, removal meconium, anastomosis	2⅛ Yrs.	10 Admissions to B.H. up to 2 years, 3 for obstruction due to adhesions, 7 for pulmonary infection 2⅛ Years—Fair	severe changes

relief of obstruction in 15 of the cases (79 per cent).

The preoperative diagnosis, associated pathology and the results of surgical treatment in our series of 37 cases are shown in Tables VI, VII and VIII. It should be noted that volvulus of the small intestine and other lesions were found in association with meconium ileus in a high percentage of the cases. It is essential that the surgeon recognize the pathology of meconium ileus as the cause of obstruction.

In our small group of cases the results have been poor. The obstruction has been extremely difficult to treat and management of the pulmonary complications has been discouraging. Our follow-up studies

are comparable to those of Schwachman and Leubner[32] in that all who survive surgery for the obstruction develop the classical picture of mucoviscidosis with evidence of generalized disease. The eventual outcome generally depends on the severity of pulmonary involvement and the success of controlling the respiratory disease with antibiotics. Twelve of the patients were relieved of obstruction but eight of these subsequently died. The results of our cases and the follow-up data of the four present survivors are summarized in Tables IX and X.

Congenital Megacolon

Swenson and Bill[33] and Hiatt[34] have demonstrated that the basic pathologic physiology in congenital megacolon, or Hirschsprung's disease, is a lack of propulsive movements of the rectum and lower sigmoid colon. This is due to congenital absence, or marked

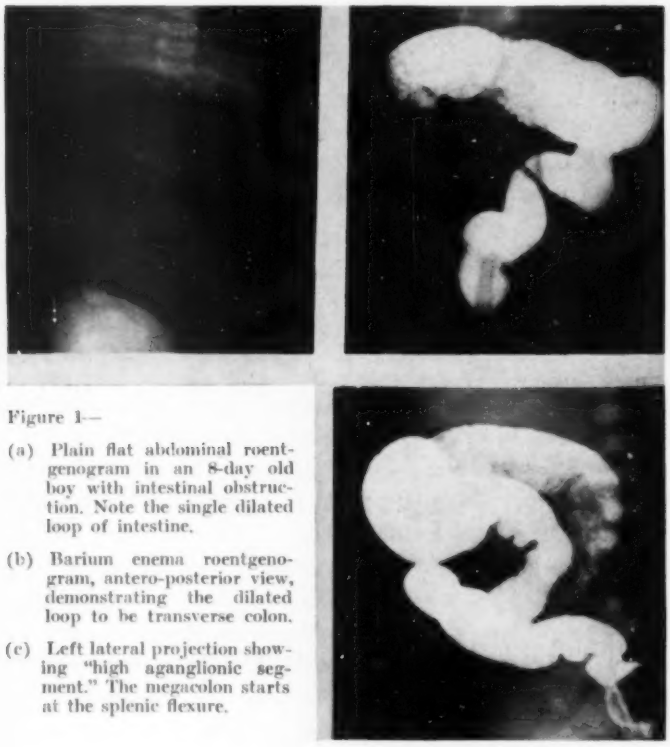

Figure 1—

(a) Plain flat abdominal roentgenogram in an 8-day old boy with intestinal obstruction. Note the single dilated loop of intestine.

(b) Barium enema roentgenogram, antero-posterior view, demonstrating the dilated loop to be transverse colon.

(c) Left lateral projection showing "high aganglionic segment." The megacolon starts at the splenic flexure.

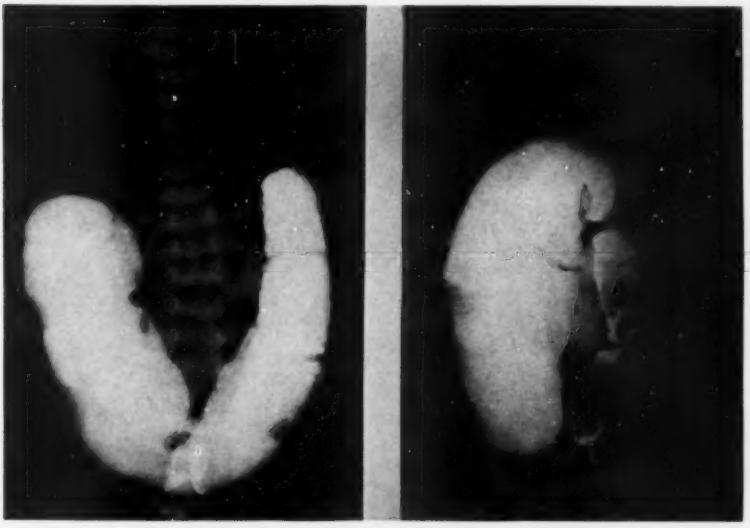

Figure 2—Roentgenograms of a 4 weeks old boy who was admitted following the administration of a barium enema at another hospital. In the lateral projection the megacolon can be seen to start in the upper descending colon.

diminution, of the ganglionic cells of Auerbach's plexus. Zuelzer and Wilson[35] have proposed calling this condition "agenesis of the myenteric plexus" and recently the term "aganglionosis" has been applied to the lesion.

There were 28 cases of intestinal obstruction due to congenital megacolon that were admitted to the Babies Hospital in the newborn period. Although the differential diagnosis between this form of obstruction and ileal obstruction is often difficult, the disease is being recognized with greater frequency in the newborn period than heretofore. As Swenson[36] has emphasized, the barium enema will easily distinguish between the two conditions and probably should be done preoperatively in all cases of intestinal obstruction in the newborn infant (Fig. 1).

The characteristic roentgen findings of megacolon above the level of aganglionosis are not clearly developed until later on, in the usual case. However, we have seen the typical features clearly demonstrated roentgenologically in the newborn period in some of our more severe cases. These may have "high segments" of aganglionosis and the mega-

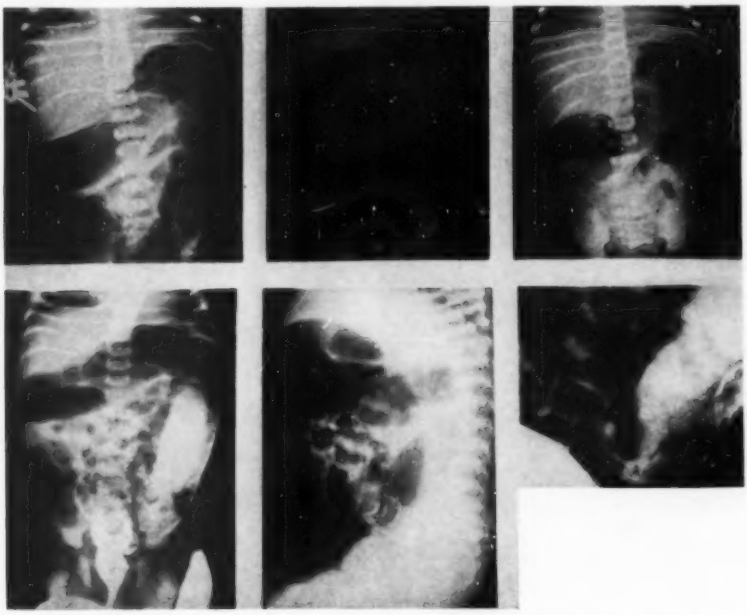

Figure 3—The upper 3 plain roentgenograms of the abdomen in the supine, erect lateral and erect antero-posterior projections were taken in a 3-day old infant and demonstrated intestinal obstruction.

The lower 3 roentgenograms, after the administration of barium by rectum, show the megacolon with the transition area in the upper sigmoid colon at 4 days of age.

colon is found in the descending colon or splenic flexure (Figs. 1, 2 and 3).

It had been our practice to treat these patients conservatively, relieving the obstruction by means of enemas and thereby avoiding colostomy whenever possible. However, from a study of our past cases and the author's more recent experience it seems wiser to advise colostomy more promptly for the newborn infant who is admitted to the hospital because of intestinal obstruction due to congenital megacolon. These are apt to be the more severe cases and conservative management may be difficult and uncertain. Colostomy is usually well tolerated. The definitive procedure of resection and "pull-through" is done at about one year of age. Table XI gives a summary of our group of cases. It should again be emphasized that this discussion concerns only those

TABLE XI.—CONGENITAL MEGACOLON

Admitted to hospital in newborn period because of obstruction			28
Responded to conservative treatment		15	
Required operation (in newborn period)		13	
Survivals			20
No operation to date (5 to 14 months)		3	
Operation performed in		17	
Resection and pull-through	15		
Colostomy (awaiting resection)	2		
Deaths			8

TABLE XII.—MEGACOLON DEATHS (8 of 28 Cases)

Onset	*Age on Admission*	*Age at Operation*	*Operation*	*Autopsy*
1. 1 day	1 day	6 days	Sigmoid colostomy	Pseudomembranous colitis (6 hours)
2. 1 day	2 days	5 days	Transverse colostomy	Anasarca, Hypoproteinemia (5 weeks)
3. 2 days	4 weeks	4 weeks	Sigmoid colostomy	Bacteremia, Anasarca, Hypoproteinemia (2 days)
4. 2 days	2 days	4 days	Transverse colostomy	Perforation of colon proximal to colostomy ? Due to irrigation catheter (4 weeks)
		2 weeks	Resection jejunum for obstruction and gangrene due to adhesions	
5. 1 day	4 weeks	—	None Died following enema	Rupture of sigmoid colon, barium peritonitis, chronic entero-colitis (5 hours after enema)
6. 1 day	3 weeks	—	None	
	10 weeks	10 weeks	Transverse colostomy	Acute membranous colitis and ileitis, bacteremia (24 hours)
7. 4 days	4 days	15 days	Transverse colostomy	
		19 months	Resection and pull-through, closure of colostomy	
		23 months	Resection jejunum for volvulus due to adhesions	
		3 years	None	Acute membranous colitis, extreme—Bacteremia, anal stricture (2 days)
8. 2 wks.	4 weeks	.....	None (unrecognized)	Acute membranous colitis (7 days)

cases of congenital megacolon which were admitted to the hospital because of obstruction in the newborn period. Cases which were seen after the neonatal period are not included in this study.

Table XII illustrates the pertinent features of the eight deaths in our group of 28 cases. Acute colitis was found at autopsy in four of the cases; chronic entero-colitis in another. Pseudomembranous colitis has been a serious complication in our experience with megacolon. One of the most severe cases was seen in a six day old boy who died six hours following colostomy (Case 1). The complication is a distressing one and will form the subject of another paper.

Other Causes of Obstruction

The other less common causes of obstruction in the newborn period are also listed in Table II. They are presented in detail elsewhere[1] and will not be discussed here. However, the following observations can be made:

Incarceration or strangulation can be a serious complication of inguinal hernia in the newborn. Of the 14 obstructed hernias, three showed strangulation of the intestine in addition to incarceration. A complication of incarcerated inguinal hernia in this age group which is not stressed sufficiently is gangrene of the testis. It was found in three of our cases and led to atrophy of the organ. The follow-up period in this group is from two months to 11 years. All patients are well, without recurrence.

Twelve of our cases of obstruction were due to congenital peritoneal bands; eight survived. One patient died at home four months after operation probably from obstruction due to adhesions. A second patient developed obstruction from adhesions four months after operation and was relieved by surgery. He has been well for 18 months. The other survivors are asymptomatic and have been followed for: six months, seven, nine, nine, 12 and 15 years.

There were ten cases of local volvulus causing obstruction. The volvulus was confined to a segment of the small intestine. In none of these cases was there associated malrotation, peritoneal bands, meconium ileus or other pathology that was responsible for the volvulus. Nine of them had gangrene and required resection. In eight cases the volvulus was of the fetal type, i.e., occurring in utero. As a result of necrosis of the base of the volvulus in the prenatal period we have encountered

two or four open or, at times, blind ends of bowel with all of the intestinal loops agglutinated in an adhesive or calcified peritonitis. These are complicated cases which test the ingenuity and patience of the surgeon. The five survivors have been followed from eight to 28 months. They are all well.

The two cases due to postoperative adhesions followed abdominoperineal repair of imperforate anus and abdominal repair of a diaphragmatic hernia. Both have been asymptomatic for over four years.

There were six cases of meconium peritonitis with obstruction in which the cause could not be determined either at operation or autopsy. The two survivors have been well for 18 months and eight years.

The three cases of obstruction due to internal herniae were paraduodenal, mesenteric defect and a defect in the falciform ligament. There were two survivors. One was seen two months following operation 10 years ago and the other only one month after operation seven months ago. Both have since been "lost" to follow-up study.

The one survivor of the intussusception group has been well three years postoperatively.

The patient with duodenal obstruction due to annular pancreas was successfully treated by duodenojejunostomy. He was mongoloid and died of pneumonia six months later.

Obstruction due to meconium "plug" was actually seen in three cases. However, in two of these the underlying cause was congenital megacolon and they are considered in that group. The one case listed in Table II was relieved of his plug and obstruction by enemas. He has been followed for six years and is perfectly normal. Clatworthy and his associates[37] have recently reported on this syndrome.

The three patients with obstruction due to multiple causes have been well for four, five and seven years since operation.

Causes of Death

Postmortem examinations were done in 81 of the 87 deaths (93 per cent). Study of the autopsy findings and of the postoperative complications revealed the following factors to be responsible for the high mortality in this group of cases:

1. *Prematurity and associated anomalies:* The incidence of prematurity (under 2500 gms.) was 17.4 per cent. It was found in 35 per cent of the atresia and stenosis group. About 20 per cent of the cases

had other associated anomalies but less than half of these were considered serious or life-threatening.

2. *Shock, dehydration, electrolyte imbalance and nutritional disturbances:* Prolonged anesthesia and surgery, non-functioning anastomoses and break-down of the anastomoses necessitating prolonged gastrointestinal suction were responsible for these complications. Although it has been difficult to properly evaluate the role of any of these factors in a given mortality, each has been the actual basis for the final and more easily defined complication which led to death.

3. *Over-hydration:* Several of the deaths, especially in the premature, were due to pulmonary edema probably resulting from the parenteral administration of excessive amounts of water and salt.

4. *Peritonitis was a common cause of death:* It occurred from leakage at suture lines or from failure to recognize and resect nonviable bowel at the time of operation.

5. *Aspiration of vomitus:* This was a common finding and could often be related to inadequate decompression of the gastrointestinal tract.

6. *Pathology incompatible with life:* As one would expect when dealing with anomalies, some of the conditions found were impossible to treat. Also, heroic efforts were made in some very small premature babies when the chances of salvage were almost nil.

7. *Delay in diagnosis and operation:* This was responsible for an indeterminate number of deaths. The delay was due to indecision on the part of the surgeon or to the late appearance of the patient for treatment.

Discussion

The mortality for the entire group of obstructions was 42 per cent. In recent years it has been lowered from 60 per cent to about 30 per cent in spite of an increasing number of premature infants that are being admitted for treatment from our premature nursery. This improvement in results can be attributed to: a better understanding of the pathology and pathologic-physiology of the lesions, improvement in supportive treatment, the principle of keeping these patients "on the dry side", the improvement in pediatric anesthesia, judicious use of the antibiotics, adequate but not prolonged period of preoperative preparation realizing that a point of "diminishing returns" is reached after a few

Figure 4—Photograph of 7-day old girl who was operated upon at 1-day for intestinal obstruction due to local volvulus and gangrene which required resection of about 40% of the proximal small intestine. A double enterostomy was performed. Note the catheter and soft rubber tubing attached to the enterostomies. By means of the attached syringe, the proximal bowel contents were effectively delivered into the distal bowel for 7 days. She required only 3 clyses during this period. The double enterostomy was closed by an anastomosis at 7 days of age.

hours, improved care of the premature infant, and a trend towards earlier recognition of obstruction. In my opinion, one of the most important factors in lowering the mortality is the routine use of adequate decompression of the gastrointestinal tract. This is especially true in cases that require anastomosis. The common denominator in many of the postoperative deaths is leakage at the suture line and this is directly or, more often, indirectly responsible for the mortality. For this reason, I believe that fewer primary anastomoses should be done and that they should be done only under ideal circumstances. If they are done, then a catheter type of enterostomy proximal to the suture line is added as this is the best means of decompression in these circumstances. Decompression of the stomach by means of a nasogastric tube is usually inadequate. In many circumstances, double enterostomy is a good method of treatment and should be used more often. Crushing of the spur of the double enterostomy with anastomosis or actual delayed

Figure 5—Photograph of the patient at 8 months of age when she weighed 15 lbs. Diarrhea persisted for 3 months after operation but at this time she was having only 2-3 formed stools daily.

primary anastomosis can be done within the next ten days. These infants tolerate double enterostomies surprisingly well provided one can provide for the delivery of the proximal bowel contents into the distal bowel (Figs. 4 and 5). This has the advantage of allowing the usually collapsed distal bowel to dilate up to a size which more nearly approaches the adequately decompressed proximal bowel at the time of anastomosis.

Summary and Conclusion

A report on 207 consecutive cases of intestinal obstruction which were admitted to the Babies Hospital during the last 17 years is presented.

The etiology, frequency of the various causes and the results are discussed. Emphasis is given to adequate follow-up study of the survivors.

The mortality was 42 per cent. It has dropped from 60 to about 30 per cent in recent years. The factors responsible for the high mortality are considered.

Although progress has been made, further improvement can be achieved by earlier recognition and treatment of these conditions through closer cooperation of the pediatrician and the surgeon.

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Discussion

Edward J. Donovan

Consulting Surgeon to Presbyterian and St. Luke's Hospitals, New York, N. Y.

In the past few days I have had the pleasure of examining with Dr. Santulli all of the material which he has presented at this meeting. Since he has discussed the various causes of intestinal obstruction in the newborn, the operation necessary to correct each cause, the mortality, follow-up results, etc., I would like to devote the five minutes allotted to me to consideration of the subject in general terms rather than repeat many of the things he has said.

Intestinal obstruction in the newborn is always a very timely subject and one that needs presentation and discussion frequently since the mortality is still too high, the diagnosis often not made as early as it should be, the findings at operation oftentimes confusing and complex and occasionally neither thoroughly understood nor completely corrected particularly in the malrotation group. Until these things are righted we can hardly expect any marked improvement in the mortality.

Delayed diagnosis presents the most serious and most frequent problem. This does not mean that the delay necessarily occurs in the hospital for in many instances the patient is not brought in until the ideal time for operation has long since passed, thus no matter how skilfully the surgery is performed it may not be possible to correct the harm caused by delayed diagnosis. It is only fair to say that some of the conditions found at operation are so complicated and require such a long operation that it is physically impossible for a baby to stand it.

We are all well aware of the fact that a newborn baby is endowed with the power to survive an amazing amount of abdominal surgery in the neonatal period, but we must never forget for one moment that there is still a very definite limit to the amount of surgery he is able to tolerate. He will resist very vigorously up to a certain point beyond which his downfall may be precipitous and unheralded. Also a baby must never be considered as a vest-pocket edition of an adult nor treated as such.

The surgical approach to the obstruction should be as direct as possible in order to avoid rough or unnecessary handling of tissue thereby preventing many postoperative adhesions while the most careful hemostasis is also essential as these babies will not stand great loss of blood. It is now taken for granted that no baby will be subjected to an abdominal operation who has not had his lost fluids restored (a matter of an hour or two), blood ready for immediate transfusion, and in cases of obstruction, his stomach empty or a stomach tube passed and gastric suction applied to it all during operation if necessary. Aspiration of gastric contents is a very serious complication in the newborn and is easily avoidable.

Most of the abdominal surgery in the first year of life is done to correct conditions due to or the direct cause of some congenital anomaly. Infection plays a very small part in the abdominal surgery during the first twelve months, but after that time it may produce

pathological conditions similar to those occurring in adult life.

What then does a complete intestinal obstruction in a newborn baby mean from the parent's point of view? It means that their newborn baby needs to have an immediate abdominal operation which may well be more than his physical condition will allow. What are the hazards and problems we have to consider when operating upon the newborn, let us say in the first or second day after birth? They are many, but the following are a few of the most important:

1. Prematurity presents a very great hazard because the premature does not have either the stamina or vitality of a baby born at term.

2. A newborn baby may have atelectasis or his lungs may not have reached complete expansion by the time surgery becomes necessary.

3. He may have already aspirated vomitus.

4. He may have other anomalies which have not yet been discovered. He may also have more than one anomaly of his gastrointestinal tract and for this reason it is always a good plan to determine the patency of the remainder of the gastrointestinal tract after the cause of the obstruction has been corrected. This is easily done by injecting saline into the lumen of the intestine distal to the obstruction.

5. There is always the chance that the condition in the abdomen is so difficult to correct that it may require a longer and more extensive operation than the infant can tolerate.

6. The amount of general anesthesia that the operation requires may be a serious handicap to survival in predisposing him to upper respiratory infections or perhaps cardiac arrest.

The diagnosis of intestinal obstruction may always be made by taking a plain plate of the abdomen in three positions if this is possible. Barium, as a medium for the x-ray, is unnecessary and often harmful and should not be used. One only needs to know that a complete obstruction exists either high or low in the abdomen to declare an immediate laparotomy necessary.

These babies suffer from all of the ills of high or low obstruction as found in adult life. In the high obstruction there is usually continuous vomiting with subsequent loss of electrolytes and dehydration but with little or no distention except perhaps that of the stomach, while in the lower obstruction type there will be vomiting of bile-stained fluid, no passage of meconium and later abdominal distention with palpable loops of bowel or visible peristalsis. However, the diagnosis should

be made before the distention is severe or loops of bowel palpable. When a newborn baby vomits bile-stained material a potential intestinal obstruction should be considered until ruled out. Duodenal obstruction above the ampulla of Vater, where there would be no vomiting of bile, occurs much less frequently.

Newborn babies as a rule are excellent candidates for carefully planned and skilfully executed abdominal operations. They will often get well in spite of the greatest odds if given half a chance.

I would like to compliment Dr. Santulli for this excellent study of one of our greatest problems in infant surgery. He has also, by painstaking labor, acquired an excellent foundation in the follow-up which is so important in all of these cases and particularly in meconium ileus as shown tonight. This is the type of study that is bound to produce improved results in the diagnosis and surgical treatment of these seriously ill babies.

CONRAD M. RILEY

Associate Attending Pediatrician, Babies Hospital, Columbia-Presbyterian Medical Center, New York, N. Y.

A combined meeting of this sort is certainly most helpful in developing the necessary team work to improve the surgical care of pediatric patients. Dr. Santulli has rendered a valuable service in presenting the Babies Hospital experience with intestinal obstruction in the newborn. Both Drs. Santulli and Donovan have emphasized how important early diagnosis is for the effective treatment of the problems. Early diagnosis is dependent on an alert pediatrician keeping the likelihood of intestinal obstruction in mind and taking the necessary steps to prove or disprove it.

I would like to emphasize what Dr. Santulli touched on briefly. Diagnosis in the full term infant is relatively simple. In the premature, however, the problem is much more difficult. These very tiny infants can occasionally have actual gangrenous segments of bowel and have little outwardly to suggest it. Contrariwise, some prematures fail to

pass meconium for two to three days and yet have no mechanical obstruction to explain this behavior. Errors in diagnosis have been and, I am afraid, will continue to be made in both directions. We can only keep on trying.

Secondly, a word about preoperative preparation and postoperative care of the newborn with intestinal obstruction. Time does not allow any detailed discussion of these important aspects of management which often fall under the supervision of the pediatrician. Let me just say in passing that we feel it important initially to evaluate the infant's state of fluid and electrolyte balance, and to get replacement fluids started before taking the baby to the operating room. We think that much valuable time may be lost if anything like complete correction of deficits is attempted before surgery is started.

With regard to postoperative care, experience at Babies Hospital has suggested that errors on the side of dehydration seem to be better tolerated than errors on the side of overhydration. In general we tend to keep the babies on a relatively small fluid intake with restricted electrolytes.

Lastly I was interested in Dr. Santulli's figures of the finding of meconium ileus as a cause of intestinal obstruction as compared with atresia and stenosis of the bowel. He showed that there were considerably more than half as many due to meconium ileus as due to atresia and stenosis. This is a higher proportion than I had expected. To a degree, I am sure, this is influenced by the considerable interest at Babies Hospital in cystic fibrosis of the pancreas. Thus newborn siblings of known cases of cystic fibrosis who get into trouble may be brought to the hospital because of the family's previous connection here. But even allowing for the slight overweighting of our figures because of this factor, the incidence of meconium ileus as a cause of neonatal obstruction is very high and the surgeon should be prepared to find such a condition frequently.

In closing I would like to emphasize again what Dr. Santulli and Dr. Donovan have already stressed: that early diagnosis is one of the most important factors in saving such babies' lives. This part of the life-saving procedure rests squarely on the shoulders of the pediatrician.

NEW YORK PATHOLOGICAL SOCIETY

Meeting of March 22, 1956 at The New York Academy of Medicine

CORRELATIONS IN CORONARY ARTERIAL DISEASE

JESSE E. EDWARDS

Section of Pathologic Anatomy,
Mayo Clinic and Mayo Foundation,* Rochester, Minnesota

THE literature on occlusive coronary arterial disease is, of course, extensive. That emanating only from members of the New York Pathological Society alone would give a complete picture. I shall, however, refer principally to pathologic material with which I have had direct contact but at the same time I recognize fully that the background of literature guides my thinking in this field. The material I shall refer to comes from a pathology service that performs necropsies on patients dying either in the hospital or at home while under the care of physicians, and necropsies done at the request of the coroner's office. This variety of circumstances which preceded necropsy on this service gives a comprehensive picture of coronary disease which may not be encountered by pathology services performing necropsies only on hospital patients or only on patients who have died under circumstances leading to medicolegal investigation.

METHOD OF STUDY

The routine of examining the heart for coronary disease on our service does not include injection techniques which have considerable merit and which have been used with great success by others. We examine the coronary arteries by making cross sections of the epicardial vessels at regular intervals varying from 3 to 5 mm. When coronary sclerosis of significant degree is found or when there is any question of the presence of myocardial ischemia, the heart is opened by making

* The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

a series of transverse slices across the ventricles. Usually four to five of these slices are made ending at a level just below the atrioventricular valves. The valves are then opened in the usual fashion. This method affords a broader view of the myocardium than the conventional method of opening the heart does.

When lesions are encountered on gross examination, sections are taken for histologic study from parts containing such lesions. When significant coronary atherosclerosis is found, sections also are taken from three specific zones each designed to spot check the tissue supplied by each of the three major coronary arteries. These sections are taken in the following manner: The ventricles are viewed as having five portions, the first being at the apex. The muscle supplied by the anterior descending coronary artery is tested by section taken through the anterior wall of the left ventricle and adjacent ventricular septum through the second slice of the ventricles from the apex. A section taken through the third slice between the two left papillary muscles is intended to test the muscle supplied by the left circumflex coronary artery. For the distribution of the right coronary artery, a section is taken through the fourth slice of the left ventricle from its posterior wall and adjacent portion of the ventricular septum. Having these sections available in each case in which coronary disease is a fact or a possibility gives one a working picture as to the nature of the cardiac muscle in regions which may not have grossly identifiable lesions. If lesions previously unsuspected are found, additional sections are made from the preserved heart.

Incidence of Significant Coronary Disease

White, Dry and I[1] studied at necropsy 600 hearts from male patients, 30 to 90 years of age. One hundred hearts were examined for each decade. These represent essentially consecutive necropsies in each particular decade of age without regard to the cause of death. The highest number of patients with significant coronary arterial narrowing by atherosclerosis (luminal narrowing of more than half) was found in the age range 50 to 59 as about 75 per cent of the men of this age had these lesions. In higher decades of age there was a smaller percentage of patients with such lesions. Among a like number of women, Ackerman, Dry and I[2] found that the peak of incidence of significant coronary sclerosis was in the decade from 70 to 79 years and it involved about 60 per cent of the patients.

My colleagues, Burchell and Berkson,[3] studied medical deaths at the Mayo Clinic over a two-year period. Coronary disease constituted 63.5 per cent of all cardiac deaths during this period.

Circumstances Preceding Necropsy in Cases of Coronary Disease

We recognize from the foregoing that significant coronary atherosclerosis is common but the clinical and pathologic manifestations of this disease are diverse. These may be considered from the point of view of the circumstances preceding necropsy in cases of coronary disease. These circumstances may be classified as follows: 1) other diseases with or without a history of angina pectoris but without a history of myocardial infarction; 2) sudden death with or without a history of angina pectoris but without a history of myocardial infarction; 3) angina decubitus; 4) clinically recognized acute myocardial infarction; and 5) clinically recognized healed myocardial infarction.

Other Diseases With or Without a History of Angina Pectoris But Without a History of Myocardial Infarction.—Many patients who are found to have significant coronary atherosclerosis at necropsy either have had no history of cardiac disease or have had angina pectoris without a history of myocardial infarction. In these patients the myocardium may show no lesions or may give evidence of healed myocardial infarction which had not been suspected clinically. The healed infarction may appear as a gross loss of myocardial substance or as so-called focal fibrosis.

The pathogenesis of the latter lesion is disputed; some give it the name "chronic infarction" with the implication that gradual loss of muscle and equally gradual replacement by connective tissue result from chronic ischemia. My view, which is contrary to this, is that at each area of focal fibrosis there has been at some time a correspondingly sized acute infarct which has gone through the orderly stages of resorption of necrotic muscle and finally of fibrous replacement.

Among patients coming to necropsy under the circumstances named are many with malignant tumors and other serious diseases in which the coronary atherosclerosis seems only an incidental feature. In other such cases the situation is not so clear in that the coronary disease may be the immediate cause of death in joining with certain manifestations of the underlying disease to cause acute myocardial ischemia and "acute death" with or without acute myocardial infarction.

Specifically, this involves patients who, for one reason or another, have a fall in blood pressure, as, for example, from bleeding duodenal ulcer, prolonged bleeding from aortic abdominal aneurysm or shock associated with surgical procedures.

Among patients with cardiac failure associated with hypertension or aortic stenosis, it is not simple clinically to determine whether or not coronary disease is a contributing factor to the cardiac failure. In certain cases it is only at necropsy that this point may be properly evaluated. Some of the hearts may show myocardial infarction which could not be established with certainty electrocardiographically. In some of these patients the myocardial infarction may have contributed through loss of muscle to the congestive cardiac failure. In other patients with hypertension or aortic stenosis, fatal acute pulmonary edema may be, in part at least, contributed by the factor of acute myocardial ischemia from the existing coronary disease.

I should like to digress for a moment on the subject of aortic stenosis and myocardial infarction. While it is generally recognized that aortic stenosis may cause myocardial ischemia and that small infarcts may be associated with this lesion, Anderson, Kelsey and I[4] found that in cases of aortic stenosis gross myocardial infarcts are associated with coronary atherosclerosis of a degree adequate to explain the infarct even in the absence of aortic stenosis.

Always forming interesting subjects for clinicopathologic conferences are those patients in whom manifestations of coronary disease are important but are not attributed clinically to diseases of the coronary arteries. Among such patients are those with acute myocardial and cerebral infarction in whom clinically only the brain is recognized as being diseased. I have encountered a case thought to be one of acute appendicitis in which the cause of symptoms proved to be infarction of the right kidney as a result of an embolus originating in a thrombus in the left ventricle of a heart with an unrecognized healed myocardial infarct. The initiation of diabetic coma as a consequence of nonapparent acute myocardial infarction is sufficiently known not to require further comment.

Sudden Death With or Without a History of Angina Pectoris But Without a History of Myocardial Infarction.—In this group are the cases of sudden death in which myocardial infarction has not been recognized clinically. These patients classically are the subjects of medicolegal

investigation. Many will not have a history of angina pectoris or of having sought medical care. Others will have had angina pectoris. Necropsy may reveal evidence of healed myocardial infarction representing a previous attack which for one reason or another had not been so designated clinically. Many will have focal myocardial fibrosis while others will have no evidence whatsoever of myocardial infarction.

The basis for the sudden death is commonly believed to reside in acute coronary occlusion. From pathologic examinations on our service, however, this belief is not justified, since only a minority of patients who die suddenly from coronary disease have coronary thrombosis or other form of acute occlusion. The usual picture is severe atherosclerosis at one or many foci in the coronary arteries without acute myocardial infarction.

In our experience only rarely does a person who is up and around and then dies suddenly have an acute myocardial infarct.

The basis for precipitation of sudden death in patients without acute coronary occlusion or acute myocardial infarction is generally conceded to be myocardial ischemia which leads to such serious arrhythmia as cardiac standstill or ventricular fibrillation.

The factors which precipitate acute ischemia in the absence of acute coronary occlusion may be related at times to unusual exertion which makes the disproportion between supply of blood to the myocardium and the demands for it understandable. In other instances, however, a ready explanation is not available for the acute ischemia leading to sudden death in patients who do not have anatomic evidence of acute occlusion of a coronary artery.

Angina Decubitus.—Patients who have had severe coronary atherosclerosis with or without myocardial infarction in the past may have a troublesome state known as "angina decubitus." These patients may have continuous angina even when at rest in bed. Frequently the existence of prolonged precordial pain leads to a suspicion of acute myocardial infarction. In fact in some patients the electrocardiogram may suggest, but not give conclusive evidence of, acute myocardial infarction. If such patients die, the pathologic examination may reveal that during the episode of angina decubitus acute myocardial infarction did not exist. The diagnosis in such cases may be "coronary insufficiency without acute infarction." Since the existence of coronary insufficiency may be taken as a manifestation of acute myocardial ischemia, the

death from which these patients may suffer may be explained by the development of one of the serious arrhythmias that may complicate acute myocardial ischemia.

Some patients who have had a history of angina decubitus before death and who have been suspected of having acute myocardial infarction may be found at necropsy to have acute myocardial infarction. The acute infarction, however, is commonly more recent than the entire episode. From such evidence, one must conclude that among patients with angina decubitus there may be clinical evidence suggesting acute infarction but infarction does not necessarily occur.

In discussions with clinicians, I have been told at times of patients with acute myocardial infarction in whom it took a week or longer for the electrocardiogram "to become positive." It is likely that in such situations, the patient, in the earlier stages of his acute disease, had coronary insufficiency without infarction, and necrosis of muscle developed later at the time when the electrocardiogram first indicated infarction.

Acute Myocardial Infarction

The pathologist sees only selected patients with acute myocardial infarction, since 85 per cent or more of these patients survive the acute attack. The fatal cases, therefore, are not representative of all cases of acute myocardial infarction, but are important, since they are the ones in which the clinician hoped for a different course.

The ischemia of the myocardium underlying the development of acute myocardial infarction may be associated 1) with acute coronary thrombosis or 2) with no anatomic evidence of acute occlusion of a coronary artery, but with chronic narrowing of a coronary artery from atherosclerosis with or without organized thrombi. In general, the infarcts which are not associated with demonstrable acute coronary occlusion do not involve the entire thickness of the wall, but are localized usually to the inner half of the myocardium; these are classified as subendocardial in nature. In them, while there may be conglomerate masses of infarcted muscle, bundles of infarcted muscle commonly alternate with ones that are not infarcted. The infarcts associated with acute coronary occlusion are, as a rule, transmural in nature, and some portion of each involves the entire thickness of the left ventricle. Usually the inner two thirds of the muscle is diffusely necrotic, whereas

the area beneath the epicardium may show alternating necrotic and non-necrotic bundles of muscle.

In the latter area as well as in the patchy type of subendocardial myocardial infarction, the pathologist has evidence of borderline supply of oxygen to the myocardium. In such areas some muscle fibers are inadequately supplied with oxygen and are necrotic, whereas others, although undoubtedly ischemic, are nevertheless supplied with sufficient oxygen to maintain viability. It is perhaps in this anatomic zone which may be termed "the twilight zone of viability" that certain of the electrocardiographic changes of ischemia associated with acute myocardial infarction take their origin.

In a consecutive series of patients dying with acute myocardial infarction, transmural infarction occurs about twice as commonly as subendocardial infarction.[5] As already stated, a pathologic series represents a selected group of cases of acute myocardial infarction. When patients are studied who have survived acute myocardial infarction, the incidence of transmural and subendocardial infarction favors the latter.

A specimen of heart containing an acute myocardial infarct is striking and has perhaps led to a false sense of security on the part of pathologists evaluating the cause of death in patients with this condition. It is simple for us to say, "the patient died of acute myocardial infarction," and feel that we have given an adequate explanation for the death. When we reflect on this, however, it is apparent that among patients dying of acute myocardial infarction, a variety of manifestations may differ from patient to patient. As we reflect further on this, it is not that the patient often dies of the infarction, but rather that he dies as a result of something happening to the muscle which is not infarcted. This is, after all, the portion of the heart which keeps the patient alive after he suffers from acute myocardial infarction, and the immediate cause of death usually resides in this noninfarcted tissue rather than in the more dramatic, necrotic muscle.

Mechanisms of death in acute myocardial infarction are not easily established. In an attempt to throw some light on this problem, my associates, McQuay, Burchell and I[6] studied 133 patients who had died with acute myocardial infarction, and we attempted to determine for each patient a type of death from which one might possibly conclude something regarding the mechanism of death. The major types of death were myocardial failure, "coronary failure" and rupture of the heart.

Less common causes were shock and thrombo-embolic complications. The majority of patients had not received anticoagulant therapy. Among the 133 cases that we studied, 80 (60 per cent) gave evidence of previous necrosis of muscle in the form of scars. In 58 of these cases the scars were typical of a previous gross conglomerate infarct. In 22 cases the previous area of infarction was patchy and of a type that might be termed "focal fibrosis."

Myocardial Failure.—Among the 133 patients studied, 57 (43 per cent) died of myocardial failure. Some patients had evidence of left ventricular failure alone as evidenced by pulmonary edema. Other patients had typical chronic congestive heart failure, considered to be right ventricular failure. Still others had both right and left ventricular failure.

Factors which influenced in a positive way the occurrence of myocardial failure were a previous infarct and an acute infarct of transmural nature. Among the 57 instances of myocardial failure associated with acute myocardial infarction, there were 18 in which heart failure was due to previous myocardial infarction, hypertension or calcific aortic stenosis and in which the acute myocardial infarct seemed to be a complication of the heart failure rather than a primary cause of it. In such instances, the loss of muscle or the infarct, of course, may intensify the failure existing before the final acute infarct developed.

Coronary Failure.—Coronary failure was designated as a type of death in 31 (23 per cent) of the 133 patients. This designation was given when patients, while convalescing from acute myocardial infarction, had episodes of recurring pain indistinguishable from those of a new myocardial infarct. The majority of these patients died suddenly and unexpectedly, and without pulmonary edema. Examination of the heart in each case revealed the acute infarct for which the patient had been hospitalized, but no more recent infarction. It is well to recognize this phenomenon, since physicians commonly imply that a new infarct is established when the patient has an attack of pain during convalescence from an acute myocardial infarct. From the pathologic evidence, these attacks of pain seem to represent ischemia of the noninfarcted myocardium or coronary insufficiency without infarction. The sudden death so common in these patients may be a result of serious arrhythmia originating in the viable ischemic myocardium.

In our group were two patients hospitalized because of acute myo-

cardial infarction in whom further acute infarction developed while they were in the hospital, but neither of these presented the clinical picture which is characteristic of patients designated as having coronary failure.

Rupture of the Heart.—Twenty (15 per cent) of our 133 patients died of rupture of the heart, 14 of the "free" wall and six of the ventricular septum. In each of these cases the acute infarct was transmural and in an area not previously affected. Women were inordinately highly represented among patients with rupture of the heart. Our limited figures give no evidence that administration of anticoagulants favored rupture. It was common for rupture to occur before the fifth day after the infarction, and in some cases the rupture occurred so soon after infarction that it could not be identified on gross examination. Histologic examination in such cases showed the earliest histologic evidence of infarction. This indicates that the infarct was only from 12 to 18 hours old when the rupture occurred.

Regarding the mechanism of rupture it is generally accepted now that the rupture does not represent a simple "blow out" of the left ventricular wall. Instead there seems to be a shearing action which initially causes a tear at the endocardium either in the peripheral portion of the infarct or at the junction of the infarct and bordering noninfarcted muscle. The next step is a dissection of blood from the left ventricular cavity through the muscle and into the epicardium. The final stage is dissection of the hematoma through the epicardium into the pericardial sac.

An uncommon type of rupture of the heart is rupture of a papillary muscle, usually the posterior, which causes mitral insufficiency. No example of this type was present in the particular series we studied.

Shock.—Shock occurred in 12 of our cases, in nine of which the infarction was associated with a surgical procedure. Pathologically, it was common to find well-established pulmonary edema in these patients.

Thrombo-embolic Complications.—In the study of the 133 patients dying of acute myocardial infarction, thrombo-embolic complications which would contribute to death were observed in eight patients, four having systemic arterial emboli and four pulmonary emboli. None of these patients had been receiving anticoagulant therapy.

In a larger study, Miller, Jordan, Parker and I[7] were concerned with 210 patients dying from acute myocardial infarction, 100 of whom also

had healed infarction. None of the patients had received anticoagulant therapy. Fifty-two (25 per cent) of the 210 patients had systemic arterial emboli or thrombi. Among these were nine in whom peripheral arterial occlusion was considered a major factor contributing to death. It is significant that not all patients with systemic arterial occlusion had thrombi in the left side of the heart. This indicates probably that in some patients with acute myocardial infarction and systemic arterial insufficiency, local arterial thrombi may be a consequence of coincidental localized arterial disease in affected organs.

Pulmonary embolism occurred in 33 (16 per cent) of 210 patients with acute myocardial infarction. In 13 patients (6 per cent), the pulmonary embolism was massive and either was an absolute cause of death or could have contributed significantly to it. In the remaining cases the pulmonary emboli appeared to be of minor significance.

The occurrence of systemic or pulmonary thrombo-embolic complications in association with acute myocardial infarction seems more likely in patients who have congestive heart failure than in those who do not, but may, nevertheless, occur in both.

Under uncommon circumstances a patient may die of hemopericardium with cardiac tamponade but without rupture of the heart. The source of the hemopericardium may be hemorrhage from the capillaries in the granulation tissue of organizing pericarditis.[8] This complication may appear in patients treated with anticoagulants as well as in those not so treated. Parenthetically, it may be stated that a hemorrhagic complication of pericarditis is not restricted to patients with myocardial infarction. We have observed it in nonspecific pericarditis as well as in the fibrinous pericarditis which follows surgical exposure of the pericardium.

Healed Myocardial Infarction.—As previously indicated, the majority of patients who have an acute myocardial infarct survive the attack, and at death at some subsequent time, a scar of that infarct is found in the myocardium. With this in mind, as a basis for learning more of the fate of patients who survive acute myocardial infarction, my associates, Achor, Futch and Burchell and I[9] studied the cases in which healed myocardial infarction was found at necropsy. We included only cases in which gross scars were found and excluded those with only focal fibrosis.

Clinical evidence of an attack of acute myocardial infarction was

present in somewhat less than half, 108, of the 250 cases in this study. The manner of death did not vary significantly between the patients with and those without clinical evidence of the previous myocardial infarction. In a general way, only about two-thirds of the 250 patients with healed myocardial infarction were considered to have died of cardiac causes. The one third in whom the cause of death was not considered to be cardiac included patients dying from malignant tumors and other noncardiac conditions. In this group were placed patients with peripheral arterial occlusion. Some of these patients may have suffered as a result of emboli from a mural thrombus within the left ventricle. In the patients considered to have died of cardiac causes, coronary disease was either the only or a contributing factor to the death. When coronary disease was considered contributory, such cardiac diseases as valvular heart disease, principally aortic stenosis, or hypertension were associated.

In the patients dying of cardiac causes, the cause of death conveniently fell into three major categories, as follows: 1) congestive heart failure without acute infarction; 2) recurrent acute myocardial infarction; and 3) "acute death."

Congestive heart failure without acute myocardial infarction occurred in 44 (18 per cent) of 250 cases. Frequently in this group, hypertension or valvular disease was associated.

Recurrent acute myocardial infarction was observed in 49 (20 per cent) of the 250 cases. The causes of death were varied and were along the lines outlined for types of death in acute myocardial infarction.

Acute death without congestive heart failure or acute infarction was the most common single type of cardiac death in patients with healed myocardial infarction; it occurred in 64 (26 per cent) of 250 cases. In this type of case, death occurred either suddenly or within 12 hours, but usually less, from the onset of acute distress. Pathologically, only the healed infarct and the associated coronary arterial disease were present without acute infarction and usually without acute coronary occlusion.

It is important to emphasize that in all patients with coronary disease, including patients with healed myocardial infarction, the existing coronary disease may be a basis for the development of acute myocardial ischemia and sudden death just as in patients with coronary disease that do not have myocardial infarction.

Comment

In the foregoing, I have attempted to indicate that significant coronary atherosclerosis is commonly observed at necropsy. The manifestations of this disease in some patients may be insignificant. When coronary disease becomes significant, it does so by the development of myocardial ischemia either as a result of acute coronary occlusion or without any anatomic evidence of acute coronary occlusion. The myocardial ischemia may cause sudden death. It may give rise to clinical episodes suggesting acute myocardial infarction, but without necrosis of muscle, or it may be responsible for death of muscle. The tendency is for patients with various manifestations of coronary disease to recover from a given episode, but in their recovery, these patients still have coronary disease and are subject to recurrent attacks of the same type or to other types.

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[DISCUSSION ON NEXT PAGE]

DISCUSSION

WILLIAM DOCK: It has been a great pleasure to have this concise and lucid review of the problem as seen in Dr. Edwards' community. Wherever we study this disease, it is a different disease. In a report from the Massachusetts General Hospital 10 per cent of their patients who died of coronary disease before anticoagulation therapy died with a ruptured heart. At the present time in that hospital rupture of the heart is twice, and hemorrhagic pericarditis is three times, as common in those who have anticoagulation therapy as in those who have not had it.[1] This sort of variation constantly confronts one in reviewing different collections of patients with a coronary disease. In Dr. Edwards' group quite a few of the patients had right-sided heart failure. In the Army Institute of Pathology,[2] right-sided heart failure did not occur under 35 years of age, and was present in 15 per cent of those 50 years or over.

Age and rupture are very interesting problems. Dr. Edwards' population may not be as old as that of the Massachusetts General Hospital study. In a Massachusetts Asylum in 80 per cent of the autopsy cases of coronary deaths the patients died of rupture.[3] The report shows that only one was in motion at the time of his death, and there was no reason to believe that violent struggling had anything to do with rupture. In the Army Institute of Pathology study it is quite obvious that violent exercise does not lead to rupture of the heart in young men. Less than 1 per cent of those under 35 years of age had rupture of the heart, so that there is an enormous variation in what the pathologist sees in different populations. The man who sees only coroner's material believes that angina and coronary disease are not related, and each one of us sees a different angle of this enormous problem. It is most instructive to see a group of cases as carefully studied as those presented by Dr. Edwards.

At the moment there is one thing which makes the clinicians concerned about one group Dr. Edwards stressed—the patients who come in with heart trouble, either very ill, or not ill, and die within the first few weeks under medical management. It appears now that half of the deaths are perhaps due to mismanagement. There are now two series of patients on record, the cases reported by Wood, Beckwith and Camp[4] from the University of Virginia and Helander's[5] from Sweden. Both deal with the death rate in groups of patients hospitalized for myocardial insufficiency or coronary disease. Wood's cases were divided into two groups, with equal proportion of cases so severe as to show signs of shock and tachycardia in each group. In both series alternate patients were kept in bed, and the other patients were managed the way this disease was treated before 1925—the patient was kept in bed if he was in shock, but as soon as he was able to use a commode or sit up for meals he was allowed to do so. The death rate was twice as high in the patients treated by the conventional method of six weeks of total rest as in those who used commodes and armchairs. Thus it is possible that many of the patients in Dr. Edwards' series might not have died had they been treated in a different way from the conventional treatment of acute myocardial infarction.

According to the method outlined in one of the leading text books of medicine in the United States, the diet for acute myocardial infarction should be chiefly eggs, custard, ice cream and milk. We have pretty good evidence that some patients have angina set off by a high fat meal. The group at the University of Pennsyl-

vania[6] studied these patients, and stated that after a high fat meal (with the blood coagulability up, and the blood viscosity up) patients have pain that they do not have at any other time. Obviously the diet mentioned above, and probably intended originally for use in typhoid fever, will hasten coronary accidents in patients kept in bed as though they had typhoid fever.

We do not always limit the salt intake. I have been interested in patients who get their initial attack of pain between midnight and six in the morning, come to the hospital with acute myocardial infarction, and at autopsy are found to have had no recent thrombosis. It seems to me quite likely that the atheromata get edematous during the night, the way one's face gets edematous during the night after a high salt intake. Recumbency without salt restriction seems hazardous. Heavy sedation, no restriction of salt intake, and no restriction of animal fat in the diet probably account for many deaths of patients kept in bed six weeks.

When the paper by Wood, Beckwith and Camp[4] came out I thought it was too good to be true. Armchair therapy is a better way to manage coronary attacks and might lower mortality 10 or 15 per cent, but 50 per cent seemed too much to expect. When Helander's paper came from Sweden and the death rate was doubled by the conventional method of treatment, I began to realize that Wood's figures were right. In some of these patients who are getting optimal classical treatment for coronary disease and yet die, with or without fresh myocardial infarcts, perhaps we ourselves must take the responsibility. If that is so, the death rate will continue to be high, but if we learn from this experience perhaps pathologists will see fewer cases. It is obvious that the better the patients are treated, the lower the percentage of "unexplained deaths" they will show. Dr. Edwards has brought us very important information on the variability of this disease. He has emphasized that myocardial infarction is not as simple as acute coronary thrombosis and its sequelae. I think we should all re-examine this problem and see if we cannot lower the death rate as it has been lowered in the cases reported by Wood and Helander. Apparently half the deaths, when we enforce six weeks of bed rest, are avoidable. Since 25 per cent of us are going to have coronary occlusions this is a message which is of great importance to us. We may live longer if we learn from the experience of Levine, Wood, and Helander.

CLARENCE E. de la CHAPELLE: I should like to congratulate Dr. Edwards for his splendid presentation of a very timely subject to which he and his associates of the Mayo Clinic have made many fundamental contributions over a period of years. Dr. Edwards will forgive me if I include a few of his colleagues whom I number among my friends, such as Arlie Barnes, Howard Burchell and Thomas Dry, among those who have contributed so much to the knowledge of the type of heart disease considered here this evening. I think he is very fortunate to have this fine group interested in the clinical aspects of his project. This kind of team work between clinicians and pathologists is essential in correlative studies.

Dr. Edwards is also to be congratulated on having made use of necropsies, not only from among the hospital patients, but also from those performed under the auspices of the Coroner's Office, for, as he states, it gives a much broader and more comprehensive picture of coronary disease. It has always been one of the "blessings" of the Pathological Laboratory of Bellevue Hospital to have necropsy material available from the Medical Examiner's Office, which shares the facilities

of that unit of the Hospital. Not infrequently some of the cardiac patients we have followed for many years as in- or out-patients die outside the hospital and come to necropsy under the aegis of the Medical Examiner's Office. Needless to say, our correlative studies are benefited by this relationship, and the material from the Medical Examiner's Office gives us an entirely different viewpoint of coronary disease than we would otherwise have.

I should also like to commend Dr. Edwards and his associates for employing a routine of examining hearts with coronary disease, which I think is very effective for the study of myocardial lesions, namely, multiple transverse sections together with frequent cross sections at regular intervals of the coronary arteries. This method is most desirable, not only when one is making the type of analysis presented here tonight, but also for correlation with electrocardiographic recordings. Although, as Dr. Edwards stated, injection and perfusion techniques which have been used by other groups have considerable merit, the value of studies based on these methods, at least as it applies to clinical and electrocardiographic correlation, is quite limited. Such studies have added much to the knowledge of the coronary arterial system, and especially as it relates to coronary anastomoses and collateral circulation, but they have a disadvantage. Histologic sections taken from such hearts may be altered by the saline or other solutions employed in the injection technique. Needless to say, microscopic study of the gross sections is an essential part of all good correlative surveys. Sections of heart muscle should be available even from those areas which may demonstrate no gross changes. By and large, I think if we are really doing correlative studies, particularly by those who are interested in the correlation of not only the clinical findings, but also the electrocardiographic findings, we should prefer this relatively simple method of multiple transverse sections.

Speaking of the value of serial or transverse myocardial sections reminds me of a piece of apparatus which I purchased some years ago while doing correlative studies at Bellevue Hospital. I had forgotten about it until yesterday noon, when during the course of conversation with Dr. Wilens and Dr. Hall, someone mentioned having recently seen a "brain-slicing machine" for $3,000. Apparently this reminded Dr. Hall that he had seen a slicing-machine in the laboratory similar to that found in delicatessen shops, and wondered what it was for. I had to confess that it was a meat-slicing machine which I had obtained second-hand from a delicatessen supply-house back in the late twenties when I first embarked on several correlative studies relating to myocardial and coronary artery diseases. Just recently, one of my associates, Dr. Charles Kossmann, who in subsequent years did some of these studies with me,[7] informed me that Dr. Sheldon and Dr. Sayen[8] of the Hospital of the University of Pennsylvania adopted this method of gross serial sectioning in 1940 and found it to be the best technique available for their very detailed and extensive studies of the heart muscle and the electrocardiogram in coronary disease during the past 15 years. They gave us credit for being the first to have employed this form of pathologic examination in analyzing the cases submitted to multiple precordial lead electrocardiograms.

There is very little that I can add to the discussion of Dr. Edwards' very complete presentation, other than to say that our material at Bellevue Hospital has been similar to that experienced at the Mayo Clinic in regard to age groups, differences in sex, the circumstances preceding death in the proven cases of coronary

atherosclerosis, as well as in the other features so well analyzed by Dr. Edwards. There are, however, variations like those which Dr. Dock mentioned in the study from the Massachusetts General Hospital. For example, our incidence of rupture of the heart at Bellevue Hospital as it pertains to the clinical services is quite low, only about 3 per cent, as contrasted to Dr. Edwards' figures of 15 per cent. That percentage went up when we also used the Medical Examiner's material, but it did not go over 6 per cent. Three-fourths of the ruptures occurred during the first week of infarction. I think Dr. Edwards' concept of the mechanism of rupture is most interesting as well as being a very plausible one.

We, too, see quite a number of cases of heart failure associated with hypertension in which it has not been possible to determine clinically with any degree of certainty whether or not underlying coronary atherosclerosis contributed to the failure, even after careful electrocardiographic studies. This is particularly so if a bundle branch block or atrial fibrillation is the main EKG finding. Not infrequently at necropsy such patients show little or no coronary disease, and the markedly hypertrophied myocardium will appear so nearly normal grossly that many around the necropsy table including clinicians and medical students will question why such a muscle has failed. The answer is obviously an inadequate coronary arterial system, as shown by the work of Roberts and Wearn.[9] Such hearts have a blood supply inadequate for the hypertrophied muscle mass, and, therefore, the slightest thing will precipitate myocardial failure, and not infrequently, coronary insufficiency without infarction. We can search these hearts by all methods and find only hypertrophied muscle fibers. We can take the same type of hypertensive, again with a confusing EKG, and at postmortem examination the pathologist may say the patient has far advanced coronary sclerosis. I think we still have a lot to learn in trying to make a correct diagnosis of occlusive coronary disease or myocardial infarction in hypertensive patients dying of congestive failure. As various EKG techniques are perfected our diagnostic acumen at the bedside will improve, but I doubt that we will ever become infallible. There are plenty of cases, and they are best demonstrated in the group Dr. Edwards showed, of healed myocardial infarcts; many of them in patients who have sustained myocardial infarcts as determined clinically but in whom over a period of months or years all signs of which have disappeared. We see the patient five years later at necropsy, having died of some other disease or possibly with the sudden death characteristic of acute myocardial ischemia, and at postmortem examination the pathologist finds the old scar which, as far as clinical or EKG evidence is concerned, gave no clue of its presence. In such cases I think our average of correct diagnosis is even poorer than in acute myocardial infarction.

We must confess that every now and then, but still far too often, we meet with patients presenting manifestations of cerebral arteriosclerosis in whom the manifestations of coronary disease have been overlooked or not attributed to the coronaries. At necropsy the myocardial infarct becomes apparent. This also holds true, as Dr. Edwards mentioned, in some cases of diabetic coma. As based on our Bellevue experience, the number of such errors can be reduced if EKG records are more frequently obtained, especially multiple ones, and if a sense of suspicion of coronary disease is maintained in every instance of cerebral vascular accident or coma.

I am glad that Dr. Edwards emphasized the erroneous but common belief that

the basis for sudden death resides in acute coronary occlusion. Our Medical Examiners, who see most of the sudden deaths which take place in New York City in individuals who are up and around, I'm sure would agree with Dr. Edwards that a fresh gross myocardial infarct is a rare occurrence in such instances and that death is undoubtedly secondary to myocardial ischemia which in turn precipitates an abnormal physiological mechanism such as ventricular fibrillation or some similar serious arrhythmia. Of course, we also meet with sudden or unexpected death amongst our hospital patients who are under treatment for fresh myocardial infarction. The basis of precipitation of sudden death in them is usually the same as in those who die without infarction, but with significant coronary sclerosis.

I would like to add, however, that careful histologic examination of multiple sections taken from the hearts of individuals dying suddenly without evidences of gross infarction, based on the technique previously described, may reveal changes indicative of ischemia of muscle fibers or muscle bundles. Most of these patients have died from six to 12 hours after the onset of initial symptoms as based on histories subsequently obtained from relatives. It is in these early cases that chemical methods are being evolved to demonstrate that there are changes in the muscle fibers or bundles which may not be reflected in the histologic sections. Many of them, of course, appear normal.

So-called angina decubitus, as mentioned by Dr. Edwards, has often caused us considerable dismay, not only in attempting to determine the underlying pathologic process, but also in treatment and prognosis. The occurrence of prolonged substernal pain at rest should properly lead to the suspicion of myocardial infarction, despite the lack of conclusive electrocardiograms. Such patients not infrequently die without showing evidences of gross infarction, although in my experience some of them do have areas of muscle necrosis, if search includes multiple gross serial transverse sections. But, as Dr. Edwards emphasizes, undoubtedly the individual has died of a physiological disorder. I liked his remark about the importance of the non-infarcted myocardium and its relation to the immediate cause of death. Maybe we are neglecting the "normal" myocardium in the individual who has myocardial infarction. I certainly would subscribe to his idea that there must be changes, possibly changes in irritability, or in contractility and conduction, or a variety of other changes in the apparently normal muscle tissue which we will learn about in the future by biochemical methods. Maybe that is the area which precipitates the abnormal mechanism which leads to sudden death.

In reference to Dr. Edwards' remarks concerning delayed positive EKG changes, I would agree that it is likely that in such situations in the earlier phases of the disease infarction secondary to the coronary occlusion has not occurred, only later developing sufficient necrosis to be recorded electrocardiographically. However, delayed or even negative EKG findings have become much less frequent since the advent of multiple lead electrocardiography. It is now almost a routine in many hospitals, as well as in private practice, to take three standard, three extremity, and six precordial leads. This has increased the chances of obtaining positive, or at least suspicious, changes, in the majority of patients subsequently shown by clinical or pathologic data to have sustained a myocardial infarct.

I was somewhat surprised to hear that in Dr. Edwards' series of patients shock was among the least common causes of death. In a series of cases from one of the services in Bellevue Hospital which I analyzed years ago,[10] shock as diagnosed at

the bedside was the most common cause of death in those dying in the first 72 hours. Unfortunately, all those individuals did not come to autopsy, and, therefore, I cannot tell you whether death was ascribed to other causes. As contrasted to these cases it was not at all common in those succumbing in the second, third, or fourth weeks of their infarction. Other modes of death outlined this evening, such as heart failure, cardiac arrhythmia, and so-called coronary failure were among the major causes of death during this later period of the illness.

It was rather interesting to note that in the Mayo Clinic cases thrombo-embolic complications were among the least common causes of death. More specifically, only eight patients among the 133 patients dying of acute myocardial infarction showed thrombo-embolic complications of such nature as to contribute to death. This is an incidence of approximately 6 per cent. If I understood correctly, when the larger series of 210 patients was analyzed, in only nine examples of peripheral arterial occlusion and 13 of pulmonary embolism were the emboli considered to have been major factors contributing to death. This represents an incidence of approximately 10 per cent. However, some 41 per cent of the total group of 210 had systemic or pulmonary emboli or thrombi. None of these patients had received anticoagulant therapy.

In a series of 200 patients with myocardial infarction which I analyzed in the Pathological Laboratory of Bellevue Hospital some years ago prior to the advent of anticoagulant therapy, 12 per cent were complicated by embolism as diagnosed clinically.[10] At necropsy about one-half of these were considered to be of major importance or contributory to death. However, only 25 per cent of the total group showed evidences of embolism or thrombosis in the systemic or pulmonary circulation, excluding, of course, intracardiac thrombi. However, the brain was not included in the majority of these necropsies. It is interesting to see what similar groups of patients who had been treated with anticoagulants might show at necropsy. The studies of Wright, Marple and Beck[11] suggest a marked difference in the incidence of extracardiac thrombo-embolic complications found in their rather small sample of necropsies (89 cases) in favor of the treated patients (41 cases) as compared to the controls (48 cases). They averaged 125 extracardiac thrombo-embolic complications (emboli and thrombi) per hundred cases examined among cases not receiving anticoagulants, but only 45 per hundred among cases receiving anticoagulants. It is their feeling that adequate anticoagulant therapy can reduce the incidence of thrombo-embolic complications to about a third of that prevailing in untreated cases of myocardial infarction.

In closing I would again like to congratulate Dr. Edwards for this highly instructive presentation of a very provocative and stimulating subject.

JESSE E. EDWARDS: I want to thank the discussers, and to say it is a real pleasure for me to come this distance and have some interchange of ideas with people in other geographic areas than my own and also with people doing clinical work.

Differences in percentage as to one type of death or another are probably intimately connected with the circumstances bringing patients to a particular institution. For example, Dr. de la Chapelle indicated that the incidence of shock in patients dying from acute myocardial infarction is significantly higher than is the incidence of shock in our series of cases, and that the incidence of rupture of the

heart is lower in his series than it is in ours. As Dr. Dock and I were sitting side by side, he said that there is probably, in general, a difference in the acuteness of the attack in which the patient is seen in one group and in another. We may talk about unselected cases, but the very fact that patients live long enough to come to us makes them a selected group. Thus, when we analyze data on one group of patients in one institution and on another group of patients in another institution, we cannot be certain that we are really talking about identical circumstances.

Dr. Dock spoke about the lower incidence of right heart failure in the Army Institute of Pathology series as opposed to our series. The Army series represents a group of young men taken into the Army, not having hypertension. They were selected for not having hypertension. Some of our patients had hypertension. Some of our patients who died of right ventricular failure were instances of patients who were in heart failure from hypertension preceding infarction. The infarction may have been a complication of heart failure precipitated by hypertension.

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ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting, April 19, 1956, at The New York Academy of Medicine

Hepatic Cirrhosis in Cystic Fibrosis of the Pancreas

WILLIAM A. BLANC and PAUL E. A. di SANT'AGNESE

Departments of Pathology and Pediatrics, College of Physicians and Surgeons, Columbia University

Small foci of biliary cirrhosis are known to occur in cystic fibrosis of the pancreas. Severe cirrhotic changes have been described in occasional cases. However, the true incidence of these lesions has been realized only recently. In addition, these changes were mostly found at autopsy and were not recognized clinically.

A group of patients in whom the lesions had progressed to a severe and distinctive type of multilobular biliary cirrhosis with portal hypertension has been recently studied in Babies Hospital. These anatomico-clinical observations prompted a survey of our autopsy material of 140 cases. An attempt was made to clarify the morphogenesis and the evolution of the liver changes.

FOCAL BILIARY CIRRHOSIS

These early and localized lesions have been observed in 32 cases and appear as small shallow stellate grooves, measuring a few millimeters in diameter. Their grayish or greenish color stands out better after formalin fixation. Their grouping and distribution are variable, though they are mostly located beneath the capsule. Late "burned out" foci appear as deep clefts. The earliest lesion was seen in a three-day old newborn with meconium ileus. Microscopically an enlarged portal space, with intact main ducts, shows numerous small ducts and cholangioles filled with inspissated eosinophilic material similar to that seen in the pancreas.

The concretions in both liver and pancreas give the same histochemical reactions. However, the material plugging the bile ductules may display a variable bile staining.

The ductules may rupture and spilling of their content in the interstitial tissue occurs. This results, whether bile is visible or not, in a massive leukocytic and histiocytic inflammation. The reticulum fibers collapse if there is necrosis of the liver cells, or may completely disappear and be replaced by granulation tissue.

The portal spaces enlarge by bile duct proliferation and progressive peripheral fibrosis. The pattern followed is that of a "trabecular" cirrhosis, typical of biliary cirrhosis.

The number of foci of biliary cirrhosis increases with the age of the patient. However, there is no simple relationship between their number, size and stage of development, and the severity of the pancreatic or pulmonary damage, and the presence or absence of hypoplasia of the gallbladder and atresia of the cystic duct. Foci at various stages of evolution are seen in the same patient and even in the same section. These findings suggest a cyclic process and the focal action of an unknown factor superimposed on an underlying diffuse physico-chemical anomaly of the secretions.

PROGRESSION TO MULTILOBULAR BILIARY CIRRHOSIS

The independent foci become joined by fine fibrous strands. Because of the initially

focal character of the lesions, cirrhotic tissue will encircle groups of preserved lobules. Secondary changes appear in the encircled lobules and, finally, a pseudo-lobular pattern develops. Seven such cases have been seen. The name of "multilobular" biliary cirrhosis with concretions has been chosen in contrast to the term "monolobular" biliary cirrhosis, as applied to the usual type of cholostatic or cholangitic cirrhosis. The three words, *multilobular, biliary,* and *concretions* define the distinctive features of the cirrhosis in fibrocystic disease of the pancreas.

MULTILOBULAR BILIARY CIRRHOSIS WITH PORTAL HYPERTENSION

Seven cases have been observed and the diagnosis has been confirmed by biopsy in five. All patients had fully manifested cystic fibrosis and symptoms of portal hypertension. The latter were the presenting symptoms in three of them. The liver was enlarged, grossly nodular and hard. The spleen was removed surgically in five cases and showed the changes characteristic of portal hypertension. The microscopic features were as follows:

1) Formation of irregular pseudolobules larger than those of typical portal cirrhosis and biliary cirrhosis, sometimes with deep clefts producing a "hepar lobatum." 2) Presence of areas of preserved lobular architecture adjacent to massive foci of bile duct proliferation with fibrosis suggesting that the lesions were initially focal. This multilobular biliary cirrhosis may be accompanied by portal lesions and changes of liver architecture by formation of pseudolobules and of regenerative nodules. 3) The presence of occasional foci of eosinophilic concretions and the absence of moderate amount of bile stasis. 4) The acute inflammation of progressive lesions.

These features distinguish them from the chronic infiltrates usually seen in portal cirrhosis of Laennec's type and from postnecrotic scarring producing the usual type of multilobular cirrhosis.

PATHOGENESIS AND ETIOLOGY

The study of morphogenesis favors the hypothesis of a primary mechanical obstruction of cholangioles and small bile ducts. The focal character of the early stage is responsible for the distinctive appearance of the cirrhosis. This picture is not duplicated by experimental or human cirrhosis induced by other known factors. Fatty metamorphosis is probably responsible for three cases of early portal cirrhosis which we have seen in cystic fibrosis of the pancreas and may be an additional factor in the etiology of multilobular biliary cirrhosis.

The rarity of this liver lesion some years ago and its increasing frequency may be due to different causes: increased life span and therefore more time to develop hepatic lesions due to focal biliary obstruction, or longer exposure to nutritional deficiency, infection or hypoxia, or injury from antibacterial agents. However, any of these single factors may be absent in individual cases. For instance, chronic infection or hypoxia were not found in two patients and furthermore were present in patients of the same age group without cirrhosis. The morphology of the liver is different from that observed in specific amino acid or protein deficiency.

Cirrhosis has not been seen in other patients receiving any of the new antibiotics for long periods of time, and therefore these do not appear to be a causative factor of cirrhosis.

The role of generalized infection and episodes of bacteremia is difficult to evaluate. It seems probable that a descending infection may enhance inflammatory changes in obstructed bile ductules.

It may be postulated that an added infection (viral hepatitis) or nutritional insult may cause an adverse response on the part of a liver which may be basically abnormal.

Age probably acts mainly by increasing the chances to develop new hepatic lesions in a progressive disease.

SUMMARY

The hepatic area must be added to the ones frequently involved in fibrocystic disease of the pancreas.

The focal hepatic lesions may progress to a pathologically distinct and widespread multilobular biliary cirrhosis with concretions. Clinically, this advanced cirrhotic process manifests itself in patients with

fibrocystic disease of the pancreas by hepatosplenomegaly, and is characterized by the symptoms of portal hypertension and by absent or only very slight icterus.

Portal hypertension may be the reason for seeking medical attention and may dominate the clinical picture.

The lesion should be known by the surgical pathologist as the liver biopsy may be an essential step of the diagnosis in some patients.*

DISCUSSION

SIGMUND L. WILENS: I am curious as to why the intraductal concretions were not bile-stained.

WILLIAM A. BLANC: The "early" concretions are usually not bile-stained. The dense concretions frequently have a faint mahogany color. The finding of true bile plugs is quite exceptional.

SIGMUND L. WILENS: Do you think that means the bile-excreting liver cells are completely destroyed before the concretions form?

WILLIAM A. BLANC: As this condition starts as a focal disease, most of the parenchyma is intact and can take care of the excretion of bile.

SIGMUND L. WILENS: Was jaundice ever a clinical manifestation?

WILLIAM A. BLANC: Not in our patients. It was reported in rare instances only and it seems most likely that the icterus of those cases was due to some superimposed condition.

SIGMUND L. WILENS: Do you think that liver punch biopsy would be a useful method of diagnosing this lesion before death?

WILLIAM A. BLANC: The diagnosis can certainly be made on a liver biopsy if this is large enough to show the typical pattern. However, both the multilobular biliary cirrhosis and the concretions should be seen before a definite diagnosis is made. When the biopsy is done during a laparotomy, we ask the surgeon to take one fragment in an area which looks relatively well preserved, and to take also a punch biopsy which will show us the changes in the central portion of the liver.

* A more complete discussion with illustrations and bibliography has been published elsewhere: di Sant'Agnese, P.E.A. and Blanc, W. A. A distinctive type of biliary cirrhosis of the liver associated with cystic fibrosis of the pancreas, *Pediatrics, 18*:387-408, 1956.

Interstitial Pneumonia in Infants

CHARLES F. BEGG and GEORGE MANI

The pathologic anatomy of interstitial pneumonia was described and the clinical aspects were briefly reviewed and correlated with morphology. The literature on the subject of interstitial pneumonia was reviewed, and etiology, pathogenesis and treatment were discussed. It was concluded that interstitial pneumonia is one of the most common causes of death in infants and that there is an urgent need for etiologic studies and an evaluation of its response to newer antibiotics.

DISCUSSION

MILTON HELPERN: I am very much interested in Dr. Begg's and Dr. Mani's paper, and I am grateful for the demonstration of these cases. I was somewhat confused by the overlap of these particular cases and some of those which in the past we used to call acute capillary bronchitis, which did have a lot of interstitial pneumonia but also bronchiolar involvement. I think this presentation tonight pretty well distinguishes these from the others. I was curious to know why

you designated those cells as fibroblasts. Was that by exclusion? It seems to me that if they are fibroblasts, some of the cases that had gone on for some time should have shown some collagen laid down by these cells. After all, how do we recognize fibroblasts?

CHARLES F. BEGG: I think none of these patients lived long enough for the production of any significant amount of collagen. You are perhaps right that exclusion helped us to identify these cells as fibroblasts; we felt that they resembled very closely the cells seen in the supporting tissues of normal alveoli, and some of them did have the spindle shape we associate with fibroblasts. Beyond that we have no definite evidence that this is what they are.

I am not sure that there is not a transition of this type of pneumonia into the acute capillary bronchitis which you mentioned, if there is a superimposed infection. I think McCordock and Muckenfuss[1] felt that way. If they superimposed a bacterial on a viral infection then they were able to get exudative bronchitis.

SIGMUND L. WILENS: I am not clear whether or not it is possible to make a clinical diagnosis in these cases, or are the infants all dead before this process is suspected to be present?

CHARLES F. BEGG: That is the answer; by the time it was thought of, the diagnosis was made at autopsy and by the microscope. I think this is a very frustrating disease, because, as the morphology shows, you cannot expect to have much in the way of x-ray signs when there is air in the alveolar spaces, or much in the way of clinical signs to give rhonchi and rales; I do not think there is much at present to give us hope of diagnosing this condition clinically. One hope I have is that this disease may be diagnosed eventually by viral studies on tissues; such studies may lead to diagnosis by complement fixation.

SIGMUND L. WILENS: You spoke of a prodromal period. Are there any signs or symptoms at this stage that would be of help in diagnosis?

CHARLES F. BEGG: In the prodromal period the patients did not act right; they were lethargic, ate poorly; six of the 11 had runny noses; vomiting and diarrhea were occasionally seen. None of these things is specific.

LOTTE STRAUSS: I should like to ask Dr. Begg whether any of the cases of interstitial pneumonia he has observed occurred in connection with outbreaks of acute respiratory illness. I recall an experience at Lebanon Hospital in 1950 when a small outbreak of an acute respiratory disorder occurred in the premature nursery, in babies one to three weeks old. Two out of five sick babies died, and the autopsy revealed pulmonary changes quite similar to those you showed this evening. Evidently we are dealing with a transmissible agent which, however, we could not isolate. Some antibody studies on the serum of the surviving babies were negative, and attempts to isolate a virus were not made. It is interesting, and perhaps a little confusing, that Pseudomonas pyocyanea was isolated from the stools and blood in some of the cases. Another, more recent case of acute interstitial pneumonia occurred in a two year old child who died shortly after admission to the emergency ward of The Mount Sinai Hospital, after a fulminating respiratory disorder with dyspnea, tachypnea and shock. This child had an acute rheumatic carditis. It seems that the agents responsible for acute interstitial pneumonia in infants are not uniform.

CHARLES F. BEGG: We have not had anything of epidemic proportions. These cases were scattered over six years and none of them seemed to have had any relationship with the other. There have been other epidemics somewhat like yours, Dr. Strauss; Adams, Green, Evans and Beach[2] reported a number of cases, but there the lesion was associated with a bronchiolar lesion. Maybe we are preventing this exudative phenomenon because so many patients have had antibiotics before they come to the hospital, so the bacterial complications of the original process may not be occurring.

Question From Audience: Do the infants run a fever, and if so, is there a relationship of it to the severity of the disease?

CHARLES F. BEGG: We have very little information on that point because so

many of the children are abruptly brought into the hospital, and what they had previously as far as fever is concerned is dependent on hearsay. In six of the 11 children the parents did say they had a fever—how much it was I do not know—and by the time they got to the hospital nine of the 11 had high fevers; two were practically dead on admission and the temperatures were not taken. The ones who survived in the hospital did have fevers.

NORMAN S. COOPER: Does your first slide indicate that 23 of 58 autopsies on children showed this lesion?

CHARLES F. BEGG: Twenty-two of 58.

NORMAN S. COOPER: The incidence then is about 40 per cent of all your autopsies on children.

DR. KARIN OESER: What age group of patients was included in this review of autopsies?

CHARLES F. BEGG: We reviewed the autopsies on all children under ten years of age, and these lesions I reported in the last series were present in two children over the age of two, all the others were less than two, and the great majority were under six months.

WILLIAM A. BLANC: Do you believe that there may be any relationship between this disease and the acute interstitial fibrosis of the lung described by Hamman and Rich[3]?

CHARLES F. BEGG: The Hamman-Rich syndrome we are not very familiar with, but there is a very extensive production of collagen, and it seems to me in many of the areas in the Hamman-Rich syndrome we can see there is probably alveolar exudate which has been organized; also it is in an older age group, and interstitial pneumonia has more of the characteristics of an acute infectious disease. Whether some of these patients might heal and eventually develop the Hamman-Rich syndrome I cannot say.

WILLIAM A. BLANC: Our experience is in some ways similar to yours. In cases of sudden death without obvious gross pathologic findings the final diagnosis is most likely to be fulminating sepsis, acute laryngo-tracheo-bronchitis or interstitial pneumonia.

CHARLES F. BEGG: I think it is comforting information to be able to give to the clinician who must explain things to the parents who may have some feeling of guilt at not having brought the children to the hospital sooner.

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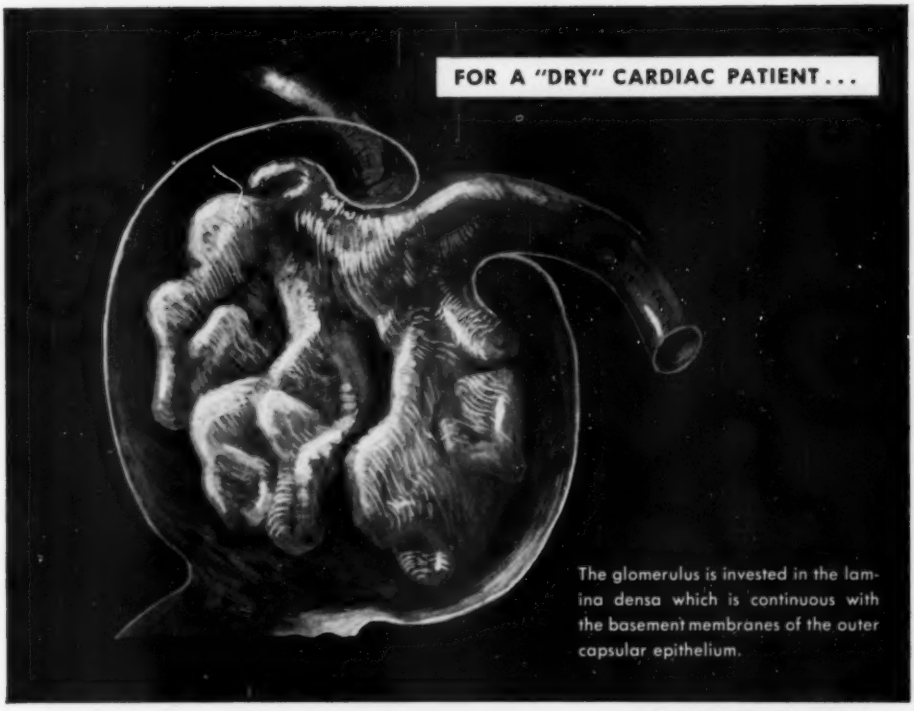
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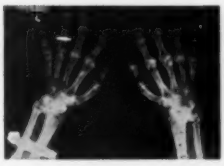

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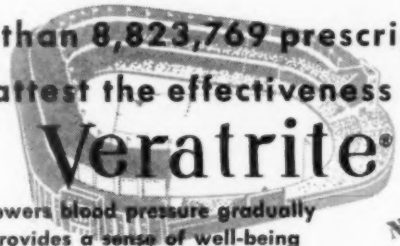

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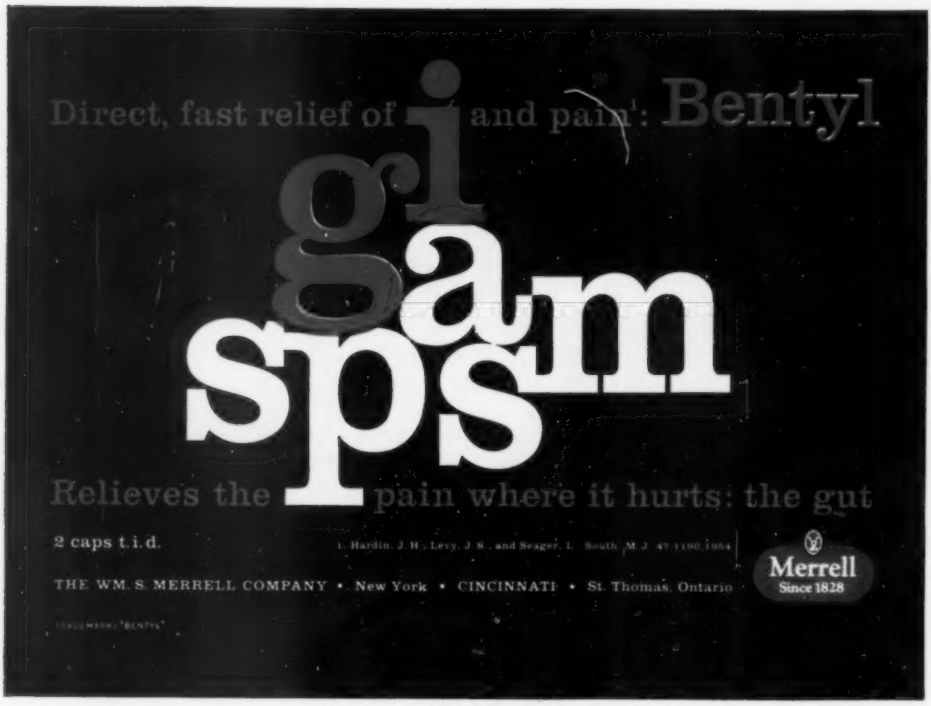
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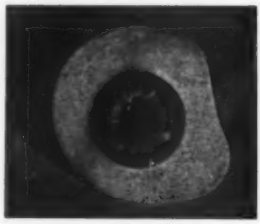

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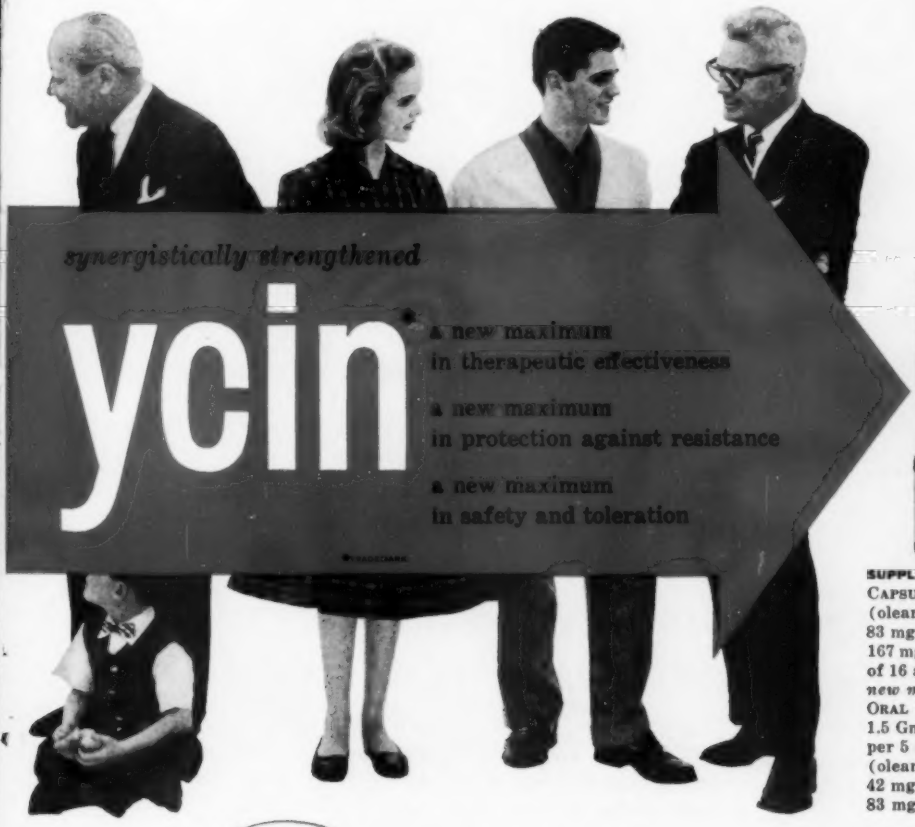
1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51. 2. Shalowitz, M., and Sarnoff, H. S.: Personal communication. 3. Shubin, M.: Personal communication. 4. La Caille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67. 5. Winton, S. S., and Cheserow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55. 6. Cornbleet, T.: Personal communication. 7. Loughlin, E. H.; Mullin, W. G.; Alcinder, L., and Joseph, A. A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.



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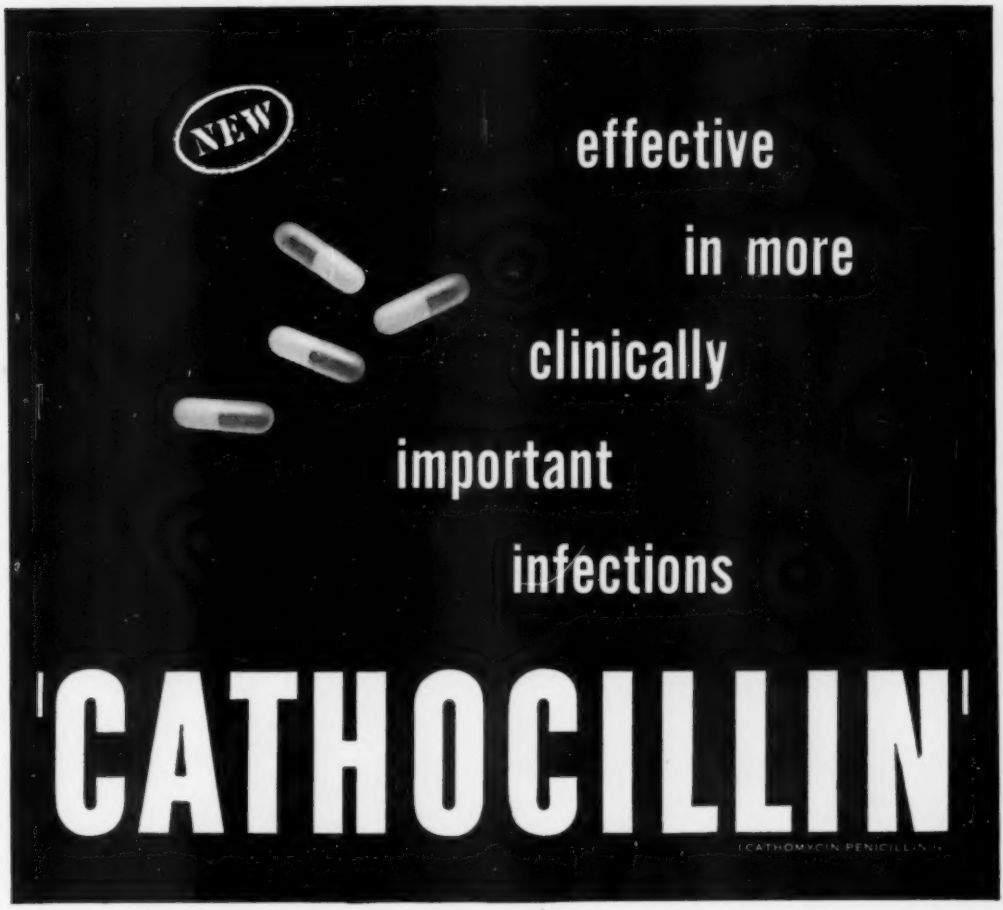

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References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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